Barrett's oesophagus and stage 1 oesophageal adenocarcinoma: monitoring and management

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British Society of Gastroenterology - Oesophageal Section Committee	Evidence review D	011		**TABLE 4** Non-endoscopic devices. Table 4 in 2.2 evidence review for non-endoscopic techniques includes the Pilonis paper. There were three parts to the paper a retrospective training and validation study and a prospective study. The prospective study was not mentioned – it is still ongoing (DELTA) which may explain why it was not included but it would be good to mention it as ongoing and data awaited.	Thank you for your comment. Table 4 has been edited to acknowledge this.
British Society of Gastroenterology - Oesophageal Section Committee	Evidence review D	011		I am surprised that non-endoscopic devices and biomarkers are not included in future research priorities.	Thank you for your comment. Clinical and molecular biomarkers have been included in the research recommendation on the optimal duration and frequency of endoscopic surveillance. See appendix F in evidence review E for further detail. The committee decided to not make a research recommendation for non-endoscopic surveillance because research is already underway on cytosponge and Esophacap. Balloon brushing is an older technique not used in current practice.. Therefore, the committee agreed these were not priority areas for future research.
British Society of Gastroenterology - Oesophageal Section Committee	Evidence review D	011		The BEST4 trial is in set up and will start recruitment in 2023. This includes a surveillance study. It is not an RCT as comparison with the gold standard endoscopy is required. Please can this be noted since we do not	Thank you for your comment. The committee are aware of this ongoing study and any newly published research will be reviewed when considering an update of the guideline. New developments within NICE guideline methodology includes the consideration of real-world evidence including registry data and the guideline manual will be updated to reflect this..

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				want to generate evidence not considered sufficient by NICE (CRUK and NIHR funded study).	
British Society of Gastroenterology - Oesophageal Section Committee	Evidence review D	012		There appears to be an error in the data on Suppl D in Table 5, p12. The sens/spec reported for the Cytosponge + biomarkers do not tally with my published data in Pilonis et al in Lancet Oncology- see Table 2. It doesn't change the recommendation as prospective data is awaited but it is important that the correct data is shown	Thank you for your comment. The data has now been corrected reflecting a separate analysis for the training and the validation cohort, in line with the analysis conducted in the paper. In line with NICE method processes (**Developing NICE guidelines: The manual**) the raw data reported in the paper have been used in 2x2 tables to calculate the sensitivity and specificity for each cohort instead of copying the published data for sensitivity/specificity reported in Table 2. Hence there is occasionally a small deviation in decimal numbers of some confidence intervals of the sensitivity/specificity we have reported compared to that of Table 2. Details of the analysis and the 2x2 tables used to calculate sensitivity/specificity can be found in Appendix I- Diagnostic evidence in Evidence review D.
British Society of Gastroenterology - Oesophageal Section Committee	Guideline	004	001	Section 1.2 Pharmacological interventions: does not mention whether PPI is recommended for chemoprevention as well as symptom control. This is a common clinical question and although this was reviewed in supplementary a statement would be helpful.	Thank you for your comment. There was insufficient evidence to recommend PPIs to prevent progression to oesophageal cancer. This is outlined in the Rationale and Impact section of the guideline and in the committee discussion section of evidence review A.
British Society of Gastroenterology - Oesophageal	Guideline	004	010	Evidence of experience in Barrett's surveillance	Thank you for your comment. The committee agree endoscopic surveillance should be carried out by staff who have the necessary qualifications and competencies.

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Section Committee					
British Society of Gastroenterology - Oesophageal Section Committee	Guideline	004	014	Frequency of endoscopic surveillance 1.3.3 This implicitly excludes short segment gastric metaplasia – it would be helpful to spell out that patients with short segments with no IM demonstrated do not require follow-up. The inclusion of these patients contributes to endoscopy bottle-necks and as noted in the evidence review the cancer risk is very low.	Thank you for your comment. The committee have added a consensus recommendation based on current practice and in line with BSG guidance that people with short segment less than 3cm Barrett's oesophagus and no intestinal metaplasia confirmed at 2 endoscopies do not require surveillance.
British Society of Gastroenterology - Oesophageal Section Committee	Guideline	005	004	>1 and <3cm – how long should surveillance continue for, - previous BSG guideance was to discharge after 2 unremarkable biopsies	Thank you for your comment. Surveillance regimes would be determined by the presence if intestinal metaplasia and length of Barrett's segment. No evidence was found for the duration of endoscopic surveillance and the committee agreed not to make a research recommendation on this. A research recommendation was made on the usefulness of clinical and molecular biomarkers to inform the optimum frequency and duration of endoscopic surveillance.
British Society of Gastroenterology - Oesophageal Section Committee	Guideline	006	006	Managing Barrett's oesophagus with dysplasia 1.5.3 The confirmation of low grade dysplasia at two separate endoscopies is questionable if you have confirmation by two pathologists with aberrant p53. There is a lot of new evidence on the role of p53 immunostaining with an impact on higher progression rates in patients with aberrant p53 (Redston Gastro 2021) and this is a straighhtforward immunostain used in NHS pathology labs.	Thank you for your comment. The committee agree P53 immunostaining is a new and potentially useful area of research. No studies are yet published on treatment decisions made based on P53. This will be flagged with the NICE surveillance team for consideration at a future update of the guideline.
British Society of Gastroenterology -	Guideline	007	007	Should there be a comment about the resection and ablation being performed in the same institution	Thank you for your comment. Delivery of services would be determined locally by the service provider.

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Oesophageal Section Committee					
British Society of Gastroenterology - Oesophageal Section Committee	Guideline	010	012	Guideline/Research Resection techniques – EMR vs ESD	Thank you for your comment. The committee are aware of research currently underway on Endoscopic Mucosal Resection (EMR) vs Endoscopic Submucosal Dissection (ESD), and therefore do not think it is necessary to add this to the research recommendation on the effectiveness of different ablation techniques for people with Barrett's oesophagus with dysplasia or stage 1 oesophageal adenocarcinoma.
British Society of Gastroenterology - Oesophageal Section Committee	Guideline	General	General	I have reviewed this document and ,as I also consider this an area of my expertise. It is in line with my expectations and evidence I am aware of, hence I support the document with no need for amendment. As I mentioned previously the replacement of CT ahead of mucosal resection to following staging EMR may be a change in clinical practice ,certainly for our mdt but I can support this recommendation.	Thank you for your comment.
Cyted Ltd	Evidence review D	012		**Table 5** In reference to: "Sensitivity= 0.67 (0.60 -0.74), Specificity= 0.89 (0.86 -0.91)" for Cytosponge (with laboratory biomarkers) to detect any grade of dysplasia/cancerThe Pilonis 2022 uses the gold-standard clinical statistical approach (area under receiver operating curve) for determining sensitivity and specificity and the results are reported in Table 2. It appears that the values in Figure 2 have been used to calculate a new sensitivity and specificity using a direct calculation but this is not the	Thank you for your comment. The data has now been corrected reflecting a separate analysis for the training and the validation cohort, in line with the analysis conducted in the paper. In line with NICE method processes (**Developing NICE guidelines: The manual**) the raw data reported in the paper have been used in 2x2 tables to calculate the sensitivity and specificity for each cohort instead of copying the published data for sensitivity/specificity reported in Table 2. Hence there is occasionally a small deviation in decimal numbers of

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				standard approach and provides inaccurate results. Table 2 actually specifies the diagnostic performance of the Cytosponge (biomarker only), biomarker + clinical factors and clinical factors only, and the sensitivity of Cytosponge (biomarker only) should be the validation cohort at 0.89 for high grade dysplasia and 0.72 for any grade dysplasia.	some confidence intervals of the sensitivity/specificity we have reported compared to that of Table 2. Overall sensitivity/specificity data do match that of Table 2 (e.g., sensitivity of 0.89 for high-grade dysplasia and 0.72 for any grade of dysplasia for the validation cohort). Details of the analysis and the 2x2 tables used to calculate sensitivity/specificity can be found in Appendix I-Diagnostic evidence in Evidence review D.
Cyted Ltd	Evidence review D	012		**Table 5** In reference to: "Sensitivity= 0.78 (0.70 -0.85), Specificity= 0.86 (0.83 -0.88)" Cytosponge (with laboratory biomarkers) to detect high-grade dysplasia/cancer The Pilonis 2022 uses the gold-standard clinical statistical approach (area under receiver operating curve) for determining sensitivity and specificity and the results are reported in Table 2. It appears that the values in Figure 2 have been used to calculate a new sensitivity and specificity using a direct calculation but this is not the standard approach and provides inaccurate results. Table 2 actually specifies the diagnostic performance of the Cytosponge (biomarker only), biomarker + clinical factors and clinical factors only, and the sensitivity of Cytosponge (biomarker only) should be the validation cohort at 0.89 for high grade dysplasia and 0.72 for any grade dysplasia.	Thank you for your comment. The data has now been corrected reflecting a separate analysis for the training and the validation cohort, in line with the analysis conducted in the paper. In line with NICE method processes (**Developing NICE guidelines: The manual**) the raw data reported in the paper have been used in 2x2 tables to calculate the sensitivity and specificity for each cohort instead of copying the published data for sensitivity/specificity reported in Table 2. Hence there is occasionally a small deviation in decimal numbers of some confidence intervals of the sensitivity/specificity we have reported compared to that of Table 2. Overall sensitivity/specificity data do match that of Table 2 (e.g., sensitivity of 0.89 for high-grade dysplasia and 0.72 for any grade of dysplasia for the validation cohort). Details of the analysis and the 2x2 tables used to calculate sensitivity/specificity can be found in Appendix I-Diagnostic evidence in Evidence review D.
Cyted Ltd	Evidence review D	076		**Table** In reference to: "results based on Cytosponge 'biomarker-positive only' for the combined cohorts have been extracted and used to calculate Sensitivity and Specificity"	Thank you for your comment. The data has now been corrected reflecting a separate analysis for the training and the validation cohort, in line with the analysis conducted in the paper. In line with NICE method processes (**Developing NICE guidelines: The manual**)

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				The Pilonis 2022 uses the gold-standard clinical statistical approach (area under receiver operating curve) for determining sensitivity and specificity and the results are reported in Table 2. It appears that the values in Figure 2 have been used to calculate a new sensitivity and specificity using a direct calculation but this is not the standard approach and provides inaccurate results. Table 2 actually specifies the diagnostic performance of the Cytosponge (biomarker only), biomarker + clinical factors and clinical factors only, and the sensitivity of Cytosponge (biomarker only) should be the validation cohort at 0.89 for high grade dysplasia and 0.72 for any grade dysplasia.	the raw data reported in the paper have been used in 2x2 tables to calculate the sensitivity and specificity for each cohort instead of copying the published data for sensitivity/specificity reported in Table 2. Hence there is occasionally a small deviation in decimal numbers of some confidence intervals of the sensitivity/specificity we have reported compared to that of Table 2. Overall sensitivity/specificity data do match that of Table 2 (e.g., sensitivity of 0.89 for high-grade dysplasia and 0.72 for any grade of dysplasia for the validation cohort). Details of the analysis and the 2x2 tables used to calculate sensitivity/specificity can be found in Appendix I-Diagnostic evidence in Evidence review D.
Cyted Ltd	Evidence review D	077		**Statistical measures** In reference to: "Sensitivity= 0.67 (0.60 -0.74), Specificity= 0.89 (0.86 -0.91)" for Cytosponge (biomarker-positive only); outcome: any grade of dysplasia or cancer The Pilonis 2022 uses the gold-standard clinical statistical approach (area under receiver operating curve) for determining sensitivity and specificity and the results are reported in Table 2. It appears that the values in Figure 2 have been used to calculate a new sensitivity and specificity using a direct calculation but this is not the standard approach and provides inaccurate results. Table 2 actually specifies the diagnostic performance of the Cytosponge (biomarker only), biomarker + clinical factors and clinical factors only, and the sensitivity of Cytosponge (biomarker only) should be the validation cohort at 0.89 for high grade dysplasia and 0.72 for any grade dysplasia.	Thank you for your comment. The data has now been corrected to reflect a separate analysis for the training and the validation cohort, in line with the analysis conducted in the paper. In line with NICE method processes (**Developing NICE guidelines: The manual**) the raw data reported in the paper have been used in 2x2 tables to calculate the sensitivity and specificity for each cohort instead of copying the published data for sensitivity/specificity reported in Table 2. Hence there is occasionally a small deviation in decimal numbers of some confidence intervals of the sensitivity/specificity we have reported compared to that of Table 2. Overall sensitivity/specificity data do match that of Table 2 (e.g., sensitivity of 0.89 for high-grade dysplasia and 0.72 for any grade of dysplasia for the validation cohort). Details of the analysis and the 2x2 tables used to calculate sensitivity/specificity can be found in Appendix I-Diagnostic evidence in Evidence review D.

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Cyted Ltd	Evidence review D	077		**Statistical measures** In reference to: "Sensitivity= 0.78 (0.70 -0.85), Specificity= 0.86 (0.83 -0.88)" for Cytosponge (biomarker-positive only); outcome: high-grade dysplasia or cancer The Pilonis 2022 uses the gold-standard clinical statistical approach (area under receiver operating curve) for determining sensitivity and specificity and the results are reported in Table 2. It appears that the values in Figure 2 have been used to calculate a new sensitivity and specificity using a direct calculation but this is not the standard approach and provides inaccurate results. Table 2 actually specifies the diagnostic performance of the Cytosponge (biomarker only), biomarker + clinical factors and clinical factors only, and the sensitivity of Cytosponge (biomarker only) should be the validation cohort at 0.89 for high grade dysplasia and 0.72 for any grade dysplasia.	Thank you for your comment. The data has now been corrected to reflect a separate analysis for the training and the validation cohort, in line with the analysis conducted in the paper. In line with NICE method processes (**Developing NICE guidelines: The manual**) the raw data reported in the paper have been used in 2x2 tables to calculate the sensitivity and specificity for each cohort instead of copying the published data for sensitivity/specificity reported in Table 2. Hence there is occasionally a small deviation in decimal numbers of some confidence intervals of the sensitivity/specificity we have reported compared to that of Table 2. Overall sensitivity/specificity data do match that of Table 2 (e.g., sensitivity of 0.89 for high-grade dysplasia and 0.72 for any grade of dysplasia for the validation cohort). Details of the analysis and the 2x2 tables used to calculate sensitivity/specificity can be found in Appendix I-Diagnostic evidence in Evidence review D.
Heartburn Cancer UK	Evidence review D	016	003 - 015	The evidence review D is relatively positive for Cytosponge compared to other non-endoscopic techniques. Our concerns about how Cytosponge is covered in the recommendations are twofold 1."the research is not mentioned in the recommendations because it is already planned" (BEST4). This stance means that the promising nature of the current evidence is underplayed. 2. there is no link in the recommendations to review D, so not likely to be reviewed.	Thank you for your comment. The committee agree the evidence for cytosponge shows it to be promising but is not robust enough with which to make a recommendation within a national guideline. This is explained within the Rationale and Impact section of the guideline, but we agree more detailed discussion is provided in the committee discussion section of evidence review D, and we have added a link to this.

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Heartburn Cancer UK	Guideline	General	General	We are concerned that neither in this guidance nor NICE GORD guidance is there any reference to the high numbers of patients with Barrett's who are undiagnosed. We feel this guidance misses the opportunity to both inform and direct research. If surveillance is worthwhile for those with Barrett's with significant changes, then why isn't increased diagnosis covered.	Thank you for your comment. Screening is outside of the remit of NICE guidance. The Gastro-oesophageal reflux disease and dyspepsia in adult's guideline includes investigations and onward referral to specialist services.
Medtronic Ltd	Evidence Review H	General	General	This evidence review does not include the recent publication from Wolfson et al. (2022) which contains data published from the HALO UK registry and includes 10yr-follow-up data. This evidence supports the long-term data for the effectiveness and durability of RFA therapy for patients with Barrett's oesophagus. This study included patients with HGD (54%) and LGD (20%) and intramucosal carcinoma (26%). References Wolfson P, Ho KMA, Wilson A, McBain H, Hogan A, Lipman G, et al. Endoscopic eradication therapy for Barrett's oesophagus–related neoplasia: a final 10-year report from the UK National HALO Radiofrequency Ablation Registry. Gastrointest Endosc [Internet]. 2022;96(2):223–33. Available from: https://doi.org/10.1016/j.gie.2022.02.016	Thank you for your comment. This paper was published after the development stage of the present guideline had been completed and therefore could not be included. Nevertheless, the committee discussed the publication of this paper and are aware of the HALO UK registry. They agree it does not add to the present guideline mainly due to the exclusion of ¾ of the population due to a lack of follow-up data.
Medtronic Ltd	Guideline	006	004	Recommendation 1.5.2 states: "Offer endoscopic ablation of any residual Barrett's oesophagus to people with high-grade dysplasia after	Thank you for your comment. The committee have not specified any one ablation technique within the recommendation for people with high grade dysplasia or T1a oesophageal adenocarcinoma

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				treatment with endoscopic resection." Medtronic accepts this recommendation. This recommendation is robust and is supported by a large body of evidence (Evidence Review H: Evidence review for the clinical and cost effectiveness of endoscopic treatments in Barrett's Oesophagus (high-grade dysplasia, stage 1 adenocarcinoma)) and we note that the evidence is in support of the clinical use of radiofrequency ablation (RFA) and argon plasma coagulation (APC). However, the draft recommendation does not specify this. The guideline stipulates on page 16, line 17, that: "The evidence indicated that both radiofrequency ablation (RFA) and argon plasma coagulation (APC) are effective in reducing the risk of recurring oesophageal lesions in people who have received an endoscopic resection for high-grade dysplasia." We believe that clear specification on the techniques recommended is particularly important to providing effective treatment for the specified patient population. Therefore, we would like to respectfully ask that the committee amend the wording of this recommendation to specify which endoscopic ablation techniques should be used, as suggested by the conclusions pertaining to the robust clinical and cost effectiveness evidence. We have suggested the following wording below:	because there is no evidence of superiority of one ablation technique over the other. The committee discussed the need for further research comparing the different ablation modalities, particularly APC and cryotherapy as the evidence is limited. The committee have made a research recommendation for a RCT to be conducted on the effectiveness of different endoscopic ablation techniques alone or in combination with endoscopic resection. This includes RFA, APC and cryotherapy. For further information see appendix J within evidence review H Endoscopic treatment.

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				"Offer radiofrequency endoscopic ablation (RFA) or argon plasma coagulation (APC) of any residual Barrett's oesophagus to people with high-grade dysplasia after treatment with endoscopic resection."	
Medtronic Ltd	Guideline	006	006	Recommendation 1.5.3 states: "Offer radiofrequency ablation to people with low-grade oesophageal dysplasia diagnosed from biopsies taken at 2 separate endoscopies. Two gastrointestinal pathologists should confirm the histological diagnosis." Medtronic welcomes this recommendation and agrees that this reflects the recommendations from international guidelines. This recommendation reflects the existing strong body of evidence for RFA therapy. The selected studies utilised within the evidence review documents clearly demonstrate the effectiveness and durability of RFA treatment for Barrett's oesophagus. However, this review does not include data published from the HALO UK registry which provides 10yr-follow-up data. This evidence supports the long-term data associated with the effectiveness and durability of RFA therapy for patients with Barrett's oesophagus. This study included patients with HGD (54%) and LGD (20%) and intramucosal carcinoma (26%). References Wolfson P, Ho KMA, Wilson A, McBain H, Hogan A, Lipman G, et al. Endoscopic eradication therapy for	Thank you for your comment. The Wolfson paper was published after the development stage of the present guideline had been completed and therefore could not be included. Nevertheless, the committee discussed the publication of this paper and are aware of the HALO UK registry. However, they agreed it does not add further information to the present guideline mainly due to the exclusion of ¾ of the population due to a lack of follow-up data.

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				Barrett's oesophagus–related neoplasia: a final 10-year report from the UK National HALO Radiofrequency Ablation Registry. Gastrointest Endosc [Internet]. 2022;96(2):223–33. Available from: https://doi.org/10.1016/j.gie.2022.02.016	
Medtronic Ltd	Guideline	007	007	Recommendation 1.6.3 states: "Offer endoscopic ablation of any residual Barrett's oesophagus to people with T1a oesophageal adenocarcinoma after treatment with endoscopic resection." Medtronic welcomes this recommendation. This recommendation is robust and is supported by a large body of evidence. However, the guideline also states on page 18 (line 28-29) and 19 (line1): "The evidence indicated that both radiofrequency ablation (RFA) and argon plasma coagulation (APC) are effective in reducing the risk of recurring oesophageal lesions in people who have received an endoscopic resection for T1a adenocarcinoma". Nevertheless, this has not been specified in recommendation 1.6.3. We believe that clear specification on the techniques recommended is particularly important to providing effective treatment for the specified patient population. Therefore, we would like to respectfully ask that the	Thank you for your comment. The committee have not specified any one ablation technique within the recommendation for people with T1a oesophageal adenocarcinoma because there is no evidence of superiority of one ablation technique over the other. The committee discussed the need for further research comparing the different ablation modalities, particularly APC and cryotherapy as the evidence is limited. The committee have made a research recommendation for a RCT to be conducted on the effectiveness of different endoscopic ablation techniques alone or in combination with endoscopic resection. This includes RFA, APC and cryotherapy. For further information see appendix J within evidence review H Endoscopic treatment.

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				committee amend the wording of this recommendation to specify which endoscopic ablation techniques have been identified as clinically robust and cost effective. We have suggested the following wording below: "Offer radiofrequency endoscopic ablation (RFA) or argon plasma coagulation (APC) of any residual Barrett's oesophagus to people with T1a oesophageal adenocarcinoma after treatment with endoscopic resection."	
Medtronic Ltd	Guideline	014	018	Medtronic recognises that NICE have reviewed the current clinical and cost-effective evidence for the use of Cytosponge as a non-endoscopic surveillance technique to collect cells within the oesophagus. NICE have acknowledged that Cytosponge is a beneficial device for patients and have identified its potential role within the current care pathway as a diagnostic device to identify individuals at risk of oesophageal cancer (MIB240). The guideline indicates that the quality of evidence to support Cytosponge as a non-endoscopic surveillance technique is "not sufficient to support a recommendation for its use at present" for the population specified within this guideline. However, Cytosponge has primarily been adopted as a non-endoscopic screening technique for the collection of cells within the oesophagus for cytological and histological analyses. The breadth of evidence for Cytosponge as a screening technique is robust and highlights the ongoing benefits for patients. The current NHSE clinical evaluation on Cytosponge as a	Thank you for your comment. Whilst acknowledging cytosponge showed benefit in the evidence available, the committee agreed it was not robust enough to recommend as a surveillance technique within a national guideline. They were aware research in this area is ongoing.. This will be flagged with the NICE surveillance team for consideration at a future update of the guideline.

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				non-endoscopic surveillance technique is in alignment with the cohort specified within this clinical guideline and is due to be published in 2023.	
Medtronic Ltd	Guideline	General	General	Medtronic would like to thank NICE for the opportunity to comment on this clinical guideline and supporting evidence review documents.	Thank you for your comment.
Medtronic Ltd	Guideline	General	General	We ask that the following newly published studies be included in the review, as they provide clinical evidence on the long-term use of radiofrequency ablation (RFA). Wolfson P, Ho KMA, Wilson A, McBain H, Hogan A, Lipman G, et al. Endoscopic eradication therapy for Barrett's oesophagus–related neoplasia: a final 10-year report from the UK National HALO Radiofrequency Ablation Registry. Gastrointest Endosc [Internet]. 2022;96(2):223–33. Available from: https://doi.org/10.1016/j.gie.2022.02.016	Thank you for your comment. This paper was published after the development stage of the present guideline had been completed and therefore could not be included. The committee has discussed the publication of this paper and are aware of the HALO UK registry. However, they agreed it does not add further information to the present guideline mainly due to the exclusion of ¾ of the population due to a lack of follow-up data.
Medtronic Ltd	Guideline	General	General	Medtronic acknowledges the breath of evidence used to create the recommendations within the guideline. Cost Effectiveness Evidence During the scoping workshop period (December 2020) Medtronic shared a published cost-effectiveness analysis (Pollit et al 2019) on the endoscopic eradication therapy (EET) for the managements of patients with low-grade and high-grade dysplasia arising in Barrett's oesophagus. This appears to have made no appearance in the economic evidence review within the guideline or evidence review documents. The analysis concluded that the EET was cost effective in comparison to endoscopic surveillance alone.	Thank you for your comment. The Haidry paper could not be included in the relevant clinical evidence review (evidence review H) as it was a non-randomised study without a comparison group and therefore did not match the review protocol. The committee had pre-specified in the review protocol that randomised-controlled trials would be included and where RCTs are not available we would only drop down to non-randomised studies with a comparison group. Before and after studies would be excluded. Details of the protocol can be found in Appendix A in the evidence review. The Wolfson paper was published after the development stage of the present guideline had been completed and therefore could not be included. Nevertheless, the

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				Clinical Evidence Although mentioned, Medtronic noted that Haidry et al (2015) was excluded from the clinical review documents published. More specifically, this publication was excluded from Evidence Review I as the population was not relevant to the review protocol (low-grade dysplasia) and Evidence Review H as it was a "non-randomised study with no comparison group". However, we believe that the prospective clinical data obtained from the UK registry is relevant and appropriate to the UK population and as a result should have been used to demonstrate the effectiveness of RFA for patients with Barrett's oesophagus. The data provided by Haidry et al (2015) is more relevant to that of Thota et al (2018) which is a retrospective observational study based in the United States. Long-term Evidence With the recent publication of the NICE Real World Evidence framework, it should be noted that there is a wealth of evidence available which could be used to demonstrate the long-term effectiveness of RFA for the management of patients with Barrett's oesophagus. The recent publication of the HALO UK registry data (Wolfson et al 2022) provides a 10-yr follow-up for patients diagnosed with dysplastic Barrett's oesophagus and receiving RFA. This study supports the clinical effectiveness of RFA, with the study consisting of 54% patients with HGD, 20% with LGD and 26% with intramucosal carcinoma.	committee discussed the publication of this paper and are aware of the HALO UK registry. They agree it does not add to the present guideline mainly due to the exclusion of ¾ of the population due to a lack of follow-up data. The Pollit paper was not included in the review as it was based on observational data. The committee had pre-specified in the review protocol that randomised-controlled trials would be included and where RCTs are not available we would only drop down to non-randomised studies with a comparison group. There was RCT data available for this review question. Additionally, the study reported the treatment efficacy for RFA. However, costs and resource use were based on RFA plus EMR. This meant that the treatment effectiveness did not align with the costs of treatment. For the two reasons outlined above, this study was not included in the review.

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				References Vicki Pollit, David Graham, Catherine Leonard, Alexandra Filby, Jessica McMaster, Stuart J. Mealing, Laurence B. Lovat & Rehan J. Haidry (2019) A cost-effectiveness analysis of endoscopic eradication therapy for management of dysplasia arising in patients with Barrett's oesophagus in the United Kingdom, Current Medical Research and Opinion, 35:5, 805-815, DOI: 10.1080/03007995.2018.1552407 Haidry, R. J., Butt, M. A., Dunn, J. M. et al. (2015) Improvement over time in outcomes for patients undergoing endoscopic therapy for Barrett's oesophagus-related neoplasia: 6-year experience from the first 500 patients treated in the UK patient registry. Gut 64(8): 1192-9 Wolfson P, Ho KMA, Wilson A, McBain H, Hogan A, Lipman G, et al. Endoscopic eradication therapy for Barrett's oesophagus–related neoplasia: a final 10-year report from the UK National HALO Radiofrequency Ablation Registry. Gastrointest Endosc [Internet]. 2022;96(2):223–33. Available from: https://doi.org/10.1016/j.gie.2022.02.016	
NHS England	Guideline	General	General	This guidance will not have any impact on clinical practice for primary care / general practice as it focuses on secondary care treatment and surveillance.	Thank you for your comment. We agree the focus of the guideline is on treatment and surveillance delivered within secondary care.
Pentax Medical	Evidence	019	General	The following comparative study was omitted from your literature review	Thank you for your comment. You are referring to the paper by Agarwal et al 2021. As listed in Appendix I, table 29, this study was excluded as per protocol, as it included

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	Review H			Comparative outcomes of radiofrequency ablation and cryoballoon ablation in dysplastic Barrett's esophagus: a propensity score-matched cohort study Histologic outcomes of EET using CBA and RFA for dysplastic BE appear to be comparable. A randomized trial is needed to definitively compare outcomes between these 2 modalities	a largely indirect population, 45% of which had low-grade dysplasia. Results relevant to people with high-grade dysplasia which was the population of interest in the present evidence review were not reported separately and therefore could not be included.
Pentax Medical	Evidence review H	019	General	Since publication of IPG682, dated 2020, we have seen the publication of further data – including the Coldplay III prospective trial Multifocal Cryoballoon Ablation for Eradication of Barrett's Esophagus-Related Neoplasia: A Prospective Multicenter Clinical Trial - PubMed (nih.gov) In a prospective clinical trial, 11 academic and community centres recruited consecutive patients with BE of 1-6 cm length and low-grade dysplasia, high-grade dysplasia (HGD), or intramucosal adenocarcinoma (ImCA) confirmed by central pathology. Patients with symptomatic pre-existing strictures or visible BE lesions had dilation or endoscopic mucosal resection (EMR), respectively, before enrolment. A nitrous oxide cryoballoon focal ablation system was used to treat all visible columnar mucosa in up to 5 sessions. Study end points included complete eradication of all dysplasia (CE-D) and intestinal metaplasia (CE-IM) at 1 year.	Thank you for your comment. This was a non-comparative study where all included participants received the same intervention and therefore did not meet the review protocol. In line with NICE method processes (**Developing NICE guidelines: The manual**) reviews for guidelines are underpinned by protocols, these are developed and agreed by the individual guideline committees using their expertise in the topic. They set out the study design for studies to be included in the evidence review before the data is collected. It had been pre-specified that for the present review, similarly to the other reviews in the guideline, we would include randomised-controlled trials (RCTs) and non-randomised studies if RCTs were not available as long as they compared different interventions. Details of the protocol can be found in Appendix A of the evidence review H. The IPG method processes differ and thus IPG often include different types of studies that do not meet our protocols.
Pentax Medical	Evidence review H	019	General	Further evidence published since IPG682 which we feel should have been included	Thank you for your comment. The IPG method processes differ from those of NICE guidelines and as a result IPG and NICE guidelines often include papers with different

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				van Munster et al. A novel cryoballoon ablation system for eradication of dysplastic Barrett's esophagus: a first-in-human feasibility study. Endoscopy 2020; 52(03): 193-201 DOI: 10.1055/a-1024-3967 This is the first clinical study to assess feasibility, safety, and efficacy of CbSAS90 for eradication of dysplastic BE. CbSAS90 was feasible and effective for ablating larger BE areas. The optimal dose for circumferential treatment that balances safety and efficacy requires further evaluation.	study design such as observational studies with no comparison group, before and after studies that were excluded from the evidence reviews of the present as per the review protocols. In line with NICE method processes (**Developing NICE guidelines: The manual**) reviews for guidelines are underpinned by protocols, that are developed and agreed by the individual guideline committees using their expertise in the topic. They set out the study design for studies to be included in the evidence review before the data is collected. It had been pre-specified for the present review, similarly to other reviews in this guideline, that we would include randomised-controlled trials (RCTs) and non-randomised studies if RCTs were not available, as long as they compared different interventions. Before and after studies would be excluded. Details of the protocol can be found in Appendix A of the evidence review H. The paper by van Munster you have kindly provided, did not meet our protocol as it was a non-comparative study where all included participants received the same intervention.
Pentax Medical	Evidence review H	019	General	Query why all the supporting evidence mentioned in IPG682 (NICE 2020) is not included within this Guideline draft. Please refer to https://www.nice.org.uk/guidance/ipg682/evidence/overview-final-pdf-8895488653: Hamade N, Desai M, Thoguluva Chandrasekar V et al. (2019) Efficacy of cryotherapy as first line therapy in patients with Barrett's neoplasia; a systematic review and	Thank you for your comment. The IPG methods process differ from those of NICE clinical guidelines and as a result IPG and NICE guidelines often include different types of papers. In line with NICE method processes (**Developing NICE guidelines: The manual**) reviews for guidelines are underpinned by protocols, these are developed and agreed by the individual guideline committees using their expertise in the topic. They set out the study design for studies to be included in the evidence review before the data is collected. It had been pre-specified that for the present review, similarly to other

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				pooled analysis. Diseases of the Esophagus, 32: 1-10 Visrodia K, Zakko L, Singh S et al. (2018) Cryotherapy for persistent Barrett's oesophagus after radiofrequency ablation: a systematic review and meta-analysis. Journal of Gastrointestinal Endoscopy 87(6), 1396- 1404 Westerveld DR, Nguyen K, Banerjee D et al. (2020) Safety and effectiveness of balloon cryoablation for treatment of Barrett's associated neoplasia: systematic review and meta-analysis. Endoscopy International Open, 18:E172-E178 Alzoubaidi D, Hussein M, Sehgal V et al. (2020) Cryoballoon ablation for treatment of patients with refractory oesophageal neoplasia after first line endoscopic eradication therapy. Endoscopy International Open, 08:E891-E899 John GK, Almario JAN, Skshintala VS et al (2017) Cryoballoon ablation for Barrett's oesophagus: A prospective single operator learning curve and timeefficiency study. Journal of Gastrointestinal Endoscopy 85(5S), AB566 Louie BE, Hofstetter W, Triadafilopoulos G et al (2018) Evaluation of a novel cryoballoon swipe ablation system in bench, porcine, and human oesophagus models. Journal of Diseases of the Esophagus 31, 1-7 Schölvinck DW, Friedland S, Triadafilopoulos G et al	reviews in this guideline, we would include randomised-controlled trials (RCTs) and non-randomised studies would be included if RCTs were not available, as long as they compared different interventions. Systematic reviews such as Hamade 2019, Visrodia 2018 and Westerveld 2020, Schölvinck 2017, Spiceland 2019 or reports of single cases such as Trindade 2019 were not eligible for inclusion based on our review protocols. The individual studies within the systematic reviews were checked for inclusion separately. Before and after studies such as Alzoubaidi 2020, John 2017, Louie 2018 where all participants received the same intervention with no comparison group would be excluded. Non-systematic reviews such as Barret 2018, Lal 2018, Overwater 2017, Parsi 2017, Wang 2020 were also not eligible for inclusion based on our protocols. Details of the protocol can be found in Appendix A of the evidence review H.

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				(2017) Balloon-based oesophageal cryoablation with a novel focal ablation device: dose-finding and safety in porcine and human models. Diseases of the Esophagus 30, 1-8, DOI: 10.1093/dote/dox019 Spiceland CM, Joseph Elmunzer B, Paros S et al. (2019) Salvage cryotherapy in patients undergoing endoscopic eradication therapy for complicated Barrett's oesophagus. Endoscopy International Open, 07: E904–E911 Trindade AJ and Canto MI (2019) Circumferential treatment of long-segment Barrett's oesophagus using the next-generation cryoballoon. Endoscopy, 51: E69-E70 Barrett M and Prat F (2018) Diagnosis and treatment of superficial oesophageal cancer. Annals of Gastroenterology, 31(3), 256-265, DOI: 10.20524/aog.2018.0252 Lal P and Thota PN (2018) Cryotherapy in the management of premalignant and malignant conditions of the oesophagus. World Journal of Gastroenyterology, 24(43), 4862-4869, DOI: 10.3748/wjg.v24.i43.4862 Overwater A and Weusten BLAM (2017) Cryoablation in the management of Barrett's oesophagus. Current opinion in gastroenterology, 33(4), 261-269 Parsi MA, Trindade AJ, Bhutani MS et al. (2017) Cryotherapy in gastrointestinal endoscopy. American Society for Gastrointestinal Endoscopy, 2(5), 89-95 DOI:	

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				10.1016/j.vgie.2017.01.021 Wang KK (2020) How I treat patients with Barrett oesophagus when endoscopic ablation fails (Gastroenterology & Hepatology, 16(2): 82-87 Since the landmark randomised trial by Shaheen et al in 2009, there have been a wealth of other well-designed clinical trials and large volume registry data which has shown RFA to be safe, effective and durable and is thus usually the first-line ablative technique in BE with dysplasia. Most international societies now recommend that ablation with RFA due to its vast data on efficacy and safety as first line therapy. Despite this, RFA has many important and relevant limitations with require addressing and there remains an unmet need in EET that require exploration of new therapies. Although CE-D rates with RFA are in excess of 90%, CE-IM rates are more variable with pooled rates of 78% (95% CI, 70%-86%). Data from the United States RFA registry noted a 20% recurrence of BE over a follow up period of 2.4 years and recurrence of dysplasia reported in 14% of those who had BE recurrence highlighting the important of achieving complete eradication of BE. Canto et al reported CE-D and CE-IM rates of 95% and 88% respectively suggesting that CbFAS (Cryoballoon Focal Ablation System) is comparably effective for neoplasia and BE eradication compared to RFA. Additionally, in patients who do not respond to RFA, particularly those with long segments of BE, there is lack of consensus on	

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				how many RFA treatments are necessary before labelling BE as being refractory to RFA. Pilot data of CbFAS in BE refractory to at least 3 treatment sessions of RFA demonstrated that CE-D and CE-IM rate of 78% and 39% with no adverse events reported. This study suggested that the CbFAS device was a viable treatment option for patients with refractory BE. There is also data to suggest that the CbFAS may have a comparable if not favourable safety profile compared to RFA. In a non-randomised comparative study of CbFAS and RFA for flat BE, van Munster SN et al reported significantly lower post-procedure pain scores (CbFAS 4 vs. RFA 22, p <0.01) and dysphagia was significantly lower with CbFAS vs. RFA. This would make sense theoretically as cryotherapy is thought to only destroy the superficial epithelium whilst sparing the deeper structures and thus having lower levels of pain and structuring compared to RFA. This is a vital issue in EET of the oesophagus where symptomatic dysphagia post treatment is an issue with rated of 7-15% reported – essentially sequential treatment with EMR and RFA can render asymptomatic patients with significant morbidity and symptoms that require further invasive intervention with endoscopic balloon dilation. Avenues to reduce this stenosis rate are needed. The pooled stricture incidence rate for RFA is 5.6% (95% CI, 4.2%-7.4%). Earlier studies investigating liquid nitrogen spray cryotherapy reported stricture rates of between 1-3%. Although a more recent study by Canto et	

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				al reported a stricture rate of 9.8% using the CbFAS system, this may be explained by the fact that patients in this study had higher rates of pre-treatment endoscopic resection which is known to increase the risk of developing strictures after RFA. More recently we have reduced our own treatment times to between 8-10 seconds which I envisage would bring down the reported stricture rate even further. An additional benefit of the CbFAS is that it can be used to treat BE within strictures which is not always possible with RFA. The rapid freeze thaw sequence of ablations with CbFAS potentially may lead to less disruption of the underlying collagen matrix that is responsible for the stenosis we see with other forms of ablative EET. This allows for targeted therapy of focal BE in a way that is not currently possible with other treatment modalities. The balloon itself has been refined such that it now has balloons in the form of a 'pear shape' and complies within the stricture with relatively low pressure within the balloon and a safety cut off only 4.5 psi (standard dilating balloon operate between 44-147 psi). This therefore significantly reduces the risk of iatrogenic perforation using the CbFAS which has not been reported in the literature to date.	
Pentax Medical	Evidence review H	034	019 - 024	Query risk of bias when relying on committee's experience of established RFA vs new techniques of cryotherapy, when combined with limited inclusion of cryoablation studies	Thank you for your comment. Only one study on cryotherapy meeting the protocol inclusion criteria was identified for this review. Where evidence is limited, the committee will draw on their experience and knowledge to reach a consensus view. As per all NICE guidelines, guideline committees are formed to reflect as far as practically possible, the range of

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					stakeholders and groups whose activities, services or care will be covered by the guideline. This committee was formed to ensure there was a balance of perspectives and experiences so as to ensure there is no bias in decision making brought by committee's views. Furthermore, in line with NICE method processes, risk of bias in the evidence is assessed on an individual study level using the appropriate standard checklist as described in (Developing NICE guidelines: The manual). As per the review protocol (see Evidence review H, Appendix A), the ROBINS-I checklist was used to assess risk of bias in studies included in the present review, by the technical team without the input of the committee. The outcome of this risk of bias was then presented to the committee alongside the evidence and taken into account in decision making. The aim of risk of bias assessment using a standard checklist depending on study design as appropriate is to ensure potential risk of bias in the evidence is identified in a systematic way and highlighted to the committee to impact the extent to which recommendations can be based on the evidence.
Pentax Medical	Evidence review H	035	012 - 015	The NICE Interventional procedure guideline documents for the use of Cryoballoon treatments for Barrett's Oesophagus and for squamous dysplasia of the oesophagus (IPG682) states that: "Further research should report patient selection, longer term follow-up and complications, including oesophageal stricture." It further states that the suggested further research "…could be in the form of randomised controlled trials or published registry data."	Thank you for your comment. The committee are aware of the recommendation within IPG 682 for registry data to be collected on the use of cryoballoon treatments, and that a database on cryoballoon ablation has been setup and the data is being collected, but this has not yet been published. IPG 682 has recommended this technique may be used within the context of research. The committee have not specified any one ablation technique within the recommendation for people with high grade dysplasia or T1a oesophageal adenocarcinoma.

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				Additional research including larger patient numbers with increased follow-up is required for a device that we are confident will be a useful addition to clinicians' armamentarium for the treatment of BE with dysplasia. Furthermore we believe it is worth mentioning that in 2019 the American Society of Gastrointestinal Endoscopy took the approach of providing practitioners with Barrett's management guidelines by bundling therapies under the umbrella of "Endoscopic eradication therapies/EET"; this was done to enable practitioners to choose more freely between RFA, cryotherapy, APC, etc, and in the hope of avoiding a situation where payers may not reimburse for some of these techniques if they were not explicitly mentioned in the guideline.	The committee have made a research recommendation for a RCT to be conducted on the effectiveness of different endoscopic ablation techniques alone or in combination with endoscopic resection. This includes RFA, APC and cryotherapy. For further information see appendix J within evidence review H Endoscopic treatment.
Pentax Medical	Evidence Review H	042	009	Only RCTs & comparative studies were included, however in IPG682 (NICE 2020), the recommendation was made to develop a registry for cryoablation which is underway but would not have been accepted in this review. A series of patients have been shown to be refractory to RFA and need an alternative solution to surgery. When innovative solutions to major clinical challenges are available, we believe an inclusion criteria beyond RCT's & direct comparison should be considered. As such, comments 6 & 7 refer to further evidence published post IPG682 in 2020, while comment 9 highlights the wider evidence base.	Thank you for your comment. The committee are aware of the recommendation within IPG 682 for registry data to be collected on the use of cryoballoon treatments, and that a database on cryoballoon ablation has been setup and the data is being collected, but this has not yet been published. The Interventional procedures guidelines follow a different process to clinical guidelines which is the reason for the inclusion of evidence that would not be considered in clinical guidelines. However recent changes to NICE methods, may allow registry data to be considered at any future update to the guideline. The recommendations are provided as guidance for NHS staff and patients. Decisions on treatments options are made between the heath professional and the patient.

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Pentax Medical	Evidence Review H	042	007	Cryotherapy as a generic search parameter, rather than cryoablation, may have resulted in the absence of relevant studies in this evidence review	Thank you for your comment. The search included the line **ablati*.ti,ab,kf.** To capture any mention of ablation or ablative as well as the line **(cryotherap* or cryosurg* or cryoablati* or cryoballoon* or cryospray*).ti,ab,kf.** which captures cryoablation and cryoablative.
Pentax Medical	Guideline	016	023 - 025	This recommendation for further research only includes RFA and APC but excludes cryotherapy. Please see comment 3. We believe this exclusion could discourage clinicians from adopting the cryotherapy technology and prevent them from and taking part in future research, trials and application studies, such as the C2 CryoBalloon Ablation International Registry led by Consultant Gastroenterologists at UCLH.	Thank you for your comment. Cryotherapy is included as one of the ablation techniques in the research recommendation on the effectiveness of different endoscopic ablation techniques in people with Barrett's oesophagus with dysplasia or stage 1 oesophageal adenocarcinoma. Further detail on the research recommendation is provided in appendix J in evidence review H.
Royal College of Nursing	Guideline	General	General	We do not have any comments on this consultation. Thank you for the opportunity to contribute	Thank you for your comment.
Royal College of Physicians and Surgeons of Glasgow	Guideline	014	024 - 026	While we do not have evidence for the use of non-endoscopic follow up of Barrett's Oesophagus, there is a national group in Scotland which was set up to deliver Cytosponge as an alternative to endoscopic follow up of Barrett's oesophagus surveillance patients which began in the summer of 2020. This was as a result of the COVID-19 pandemic in the presence of an already struggling endoscopy service with a demand-supply mismatch. This Cytosponge process is now established. We have been closely auditing the first out-of-trial-setting use of this technology. We hope our experience contributes to the literature and informs future guidelines. Nearly 1000 Cytosponge procedures have been performed in Barrett's patients in Greater Glasgow and Clyde Health Board with	Thank you for your comment. The committee are aware of the use of Cytosponge in Scotland. This will be flagged with the NICE surveillance team for consideration at a future update of the guideline..

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				the total number of Cytosponge procedures across Scotland now at around 4,500.	
Royal College of Physicians and Surgeons of Glasgow	Guideline	General	General	The Royal College of Physicians and Surgeons of Glasgow although based in Glasgow represents Fellows and Members throughout the UK. While NICE has a remit for England (where 50% of our UK membership is based), many of the recommendations are applicable to all devolved nations including Scotland. They should be considered by the relevant Ministers of the devolved governments. The College is in general supportive of the Guideline Barrett's oesophagus and stage 1 oesophageal adenocarcinoma: monitoring and management.	Thank you for your comment.
The Society and College of Radiographers	Guideline	General	General	Non-surgical treatment for T1b oesophageal 2 adenocarcinoma 3 1.7.1 Consider radiotherapy (alone or in combination with chemotherapy) for 4 people with T1b oesophageal adenocarcinoma at high risk of cancer 5 progression (for example, incomplete endoscopic resection, or evidence 6 of lymphovascular invasion or deep submucosal invasion (more than 500 7 micron) on histological examination of endoscopic resection specimens) 8 and who are unfit for oesophagectomy. 9 1.7.2 Offer endoscopic follow-up to people who have received radiotherapy for 10 T1b oesophageal adenocarcinoma More detail around the 'consideration' process and criteria	Thank you for your comment. We think the current wording of the recommendation provides enough detail to guide the clinician on the non-surgical treatment for T1b oesophageal adenocarcinoma. As this is standard practice the committee do not agree the further detail you suggest is needed in the recommendation, but this has been described within the discussion section of the guideline.

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				for the MDT could be beneficial to ensure parity of opportunity for patients in this category. It is stated in the section ' why the committee made the recommendations ': 10 In the absence of evidence to guide decision making, the committee drew upon their 11 clinical experience to make a recommendation on non-surgical treatment for T1b 12 oesophageal adenocarcinoma. 13 Using radiotherapy alone or in combination with chemotherapy to treat oesophageal 14 adenocarcinoma is current practice. 15 The committee agreed that radiotherapy alone or in combination with chemotherapy 16 would be appropriate for people with T1b oesophageal adenocarcinoma at high risk 17 of cancer progression as it is likely to reduce the risk of recurrence. They noted that 18 chemotherapy alone is not a definitive treatment. The fact that this is standard care and chemotherapy alone is not definitive could be actually detailed	

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

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