National Institute for Health and Care Excellence

IP1507 and IP1799 Balloon cryoablation for Barrett's oesophagus or for squamous dysplasia of the oesophagus

IPAC date: 10 October 2019

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Company PENTAX Medical	**1.1**	The NICE Interventional procedures consultation documents for the use of BC for Barrett's oesophagus and for Squamous dysplasia of the oesophagus recommend that this procedure only be used in the context of research due to "evidence on the safety and efficacy of balloon cryoablation … [being] inadequate in quantity and quality" (1) However, it is clear that interventional procedures with applications based on evidence with similar quality and quantity have been approved for the treatment of Barrett's Oesophagus with either normal arrangements or special arrangements. Several of the IPGs that were referenced as existing evidence were based on a similar quality and quantity of research, e.g. IPG350 [should be IPG497] was approved for Special Arrangements and was based on three case series on a total of 62 patients. It is our firm belief that BC for Barrett's Oesophagus and/or squamous dysplasia should also be awarded a recommendation to be used with either special arrangements or normal arrangements. The evidence included in the Interventional Procedures Consultation Document has clearly demonstrated that balloon cryotherapy is an effective treatment for Barrett's oesophagus and squamous dysplasia; use of balloon cryotherapy can achieve complete endoscopic and histologic eradiation of intestinal metaplasia and dysplasia for low-, moderate-, and high-grade intraepithelial dysplasia. Balloon cryotherapy's efficacy for the treatment of	Thank you for your comment. The Committee has considered this comment but decided not to change the recommendation. The Committee makes recommendations based on its assessment of the evidence on the efficacy and safety of that individual interventional procedure and it does not evaluate comparative effectiveness of different procedures for the same indication.

			Barrett's oesophagus is not statistically different to radiofrequency ablation, an intervention which was approved with special arrangements for squamous dysplasia of the oesophagus and normal arrangements for Barrett's oesophagus. As radiofrequency ablation is the established treatment it is reasonable to approve an alternative intervention which is as effective while being associated with less pain and less use of pain medications(5). This would be particularly valuable to patients for whom radiofrequency ablation is either ineffective or poorly tolerated. The safety of balloon cryotherapy is similar to the devices in the IPGs identified as providing related NICE guidance. While a wide range of adverse events were reported in the evidence which was included in the Interventional Procedures Consultation Document, the vast majority of these were minor adverse events which were treated with straightforward management or did not require particular treatments or interventions. Furthermore, balloon cryotherapy was associated with pain of less severity and shorter duration than radiofrequency ablation, which is the established treatment. As BC is as safe and less painful than radiofrequency ablation it should be available as a potential intervention for the management of Barrett's Oesophagus and squamous dysplasia of the oesophagus. Based on the safety and efficacy of BC for Barrett's Oesophagus and squamous dysplasia of the oesophagus and the relative safety and efficacy of alternative treatments for these indications that have been previously approved by NICE in IPGs we believe that this treatment should be recommended for use with Special Arrangements or Normal Arrangements.  Pentax comments GID-IPG10127 .docx  Pentax comments GID-IPG10139 .docx	
2	Consultee 1 Company PENTAX Medical	**1.1 & 1.3**	<u>UK/European Registry</u> The NICE Interventional procedures consultation documents for the use of BC for Barrett's Oesophagus and for squamous dysplasia of the oesophagus	Thank you for your comment. NICE has contacted Dr. Haidry and has advised him on NICE's

			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.” Pentax have already sponsored the setting up of a UK oesophageal BC registry to record the therapy and outcomes of patients who are undergoing the treatment for early oesophageal neoplasia. The refinement of the protocol and the creation of the database is about to commence and the registry is due to come online in late 2019. It is being established and maintained by the Gastroenterology department at University College London Hospital under the guidance of Dr. Haidry who already runs the longstanding radiofrequency ablation registry. Participation in the registry will be mandatory for all users of BC in the UK. As a condition for joining the registry the contributing sites will all need to be centres of excellence for upper gastrointestinal endoscopy and will need to participate in training for the administration of BC therapy, to be organised and delivered at University College London Hospital. In this way the quality of both therapy and registry data can be ensured. There is also already widespread interest from other European countries to participate in the registry program.	criteria for registries (as outlined in the IP programme manual). NICE can only recommend data collection in registries once they are in existence. If data are collected by registries which meet NICE’s criteria, NICE would be able to consider that evidence should it update its guidance in the future.
3	Consultee 1 Company PENTAX Medical	**General**	Training for the Use of BC The Pentax BC ablation system comprises a combination of well-established modalities and techniques that are already familiar to any experienced oesophageal endoscopist. These techniques such as the use of through-the-scope balloons, tissue visualisation and targeting, and mucosal ablation. However, as the system is not completely intuitive thus requires the user to be expert in oesophageal endoscopy in addition to specific training. Training for BC consists of instruction to make the user familiar with the BC system components, how to operate the equipment, treatment methodology and parameters as well as practical tips and tricks. Training is ideally	Thanks for your comment.

			conducted as hands-on benchtop instruction with the support of case videos. This is followed by performing a number of cases while supported by an experienced trainer. Data suggests that the learning curve flattens out at 18 cases (13) but, to date in Europe, unsupervised cases have not been performed before completion of at least 20 supervised cases. It is most common that the endoscopist will have performed 30-40 supervised cases before performing a BC unsupervised. As part of the UK/European Registry a masterclass course for BC treatment will be established at University College London Hospital and this will be mandatory for all participating UK centres.	

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IPAC date: 9 April 2020

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
4	Consultee 2 Healthcare professional NHS Hospital	**General**	Many thanks for taking the time to review and provide consultation on "balloon cryoablation for Barrett's oesophagus (BE) or for squamous dysplasia of the oesophagus". I am hopeful that you will find my comments useful given my wealth experience in the field of early oesophageal neoplasia and endoluminal therapy and practical experience of the cryoballoon focal ablation system (CbFAS) device itself. I have been fortunate enough to be the first clinician in the UK to use the technology and continue to lead and publish on several studies exploring the intervention in the treatment of early oesophageal neoplasia. I have divided my comments into those concerning the treatment of dysplastic Barrett's oesophagus and squamous dysplasia of the oesophagus separately.	Thank you for your comment.

5	Consultee 2 Healthcare professional NHS Hospital	**IP1507 general**	**Barrett's oesophagus with dysplasia** The ultimate goal of endoscopic eradication therapy (EET) for BE with dysplasia is resection of all visible dysplasia followed by field ablation of residual BE with the hope of achieving not only complete eradication of dysplasia (CE-D) but also intestinal metaplasia (CE-IM). 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 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 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.	Thank you for your comment. The committee has considered this comment – 2 relevant studies identified by the consultee: Canto et al. (2018) was included in table 2 and Alzoubaidi et al. (2020) has been added to the appendix.
6	Consultee 2 Healthcare professional NHS Hospital	**IP1507 general**	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	Thank you for your comment. The committee has considered this comment – 2 relevant studies identified by the consultee: Van Munster et al.

			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 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.	(2018) and Canto et al. (2018) were included in table 2.
7	Consultee 2 Healthcare professional NHS Hospital	**IP1507 general**	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.	Thank you for your comment. The committee's decision is based on available evidence and NICE would consider new evidence once it is published.
8	Consultee 2 Healthcare professional NHS Hospital	**IP1799 general**	**Oesophageal squamous cell neoplasia (ESCN)** Moderate (MGIN) and high-grade intraepithelial neoplasia (HGIN) are both indications for EET to reduce the risk of oesophageal squamous cell cancer. As with dysplastic BE, all non-flat lesions should be resected with either EMR or ESD. The dilemma of delivering local therapy to ESCN is the higher risk of loco regional lymph node metastases once the neoplasia extends to the deep mucosa or submucosa. Staging is therefore vital and tissue acquisition with resection is far more important that in BE due to the fact that accurate	Thank you for your comment. The committee has considered this comment – 2 relevant studies identified by the consultee: Ke et al. (2019) and

			staging is possible to prognosticate long term outcomes. Tissue destruction with ablation for ESCN is therefore challenging and does not offer this vital staging information for ESSCN. EMR ad ESD are however are both complex interventions with prolonged procedures and significant complication rates including bleeding and stricture formation in more than 10% of patients. Tissue destruction and ablation of squamous dysplasia would therefore seem an attractive alternative to endoscopic resection in select cases where there is endoscopic confidence that the neoplasia is very superficial and does not carry the risk of deep invasion. Yu X et al published encouraging data evaluating RFA in the treatment of 78 patients ECSN reporting an encouraging complete remission (CR) rate at 12 months of 86%. Despite this, RFA has been reported to have a stricture rate as high as 22% in patients with ESCN which thereafter can be challenging to treat particularly if they contain neoplasia. Canto et al published an early feasibility study using the CbFA device to treat ESCN in 10 patients (LGIN – 2, HGIN – 7, Post EMR - 1) and reported CR in all patients at 3 and 11 months. In this study, 2 patients (20%) developed a stricture which was treated with endoscopic dilatation. A more recent, larger prospective study by Key et al investigated the CbFA device to treat flat MGIN and HGIN and reported a CR rate in 76/78 (97%) at 12 months. Despite a higher number of median application than Canto et al (5 vs 4), no patients in this study developed strictures and the median pain score after 48 hours was only 1/10 which is significantly lower than RFA. These two studies provide encouraging data on the use of the CbFAS device for the treatment of flat ESCN.	Canto et al. (2018) were included in table 2.
9	Consultee 2 Healthcare professional NHS Hospital	**1.1**	**Summary** In my experience the procedure itself is relatively straightforward and quick to perform. Due to the fact that the device is operated through the working channel of the endoscope it avoids multiple intubations and more time efficiency and control. Canto et al reported an impressive average baseline procedure time of only 33.5 minutes in segments of BE more than 6cm which is in line with our own personal experience. The portability of the CbFAS	Thank you for your comment. The committee has considered this comment but decided not to change the recommendation. The Committee makes recommendations based on its

			system is appealing as is the non-requirement for a generator or console which affords obvious economic advantages compared to RFA. Earlier case series in particular, reported device malfunction relating to diffuser rotation and false pressure readings within the balloon. These issues were overcome when a separate device was used. Despite this, we have been working closely with the manufacturer who have refined the balloon and inflation system further to limit the likelihood of these events occurring in the future. In summary, I am confident that the CbFAS is a safe, effective and relatively straight forward treatment strategy for ablation of BE with dysplasia. Prospective studies led by our group will report a greater volume of data in coming months to consolidate this opinion. Research to date has suggested a comparable safety and efficacy profile to RFA but with lower pain scores and perhaps a lower stricture rates which may perhaps make this treatment more acceptable to patients. The ability to focus therapy within strictures and areas that would otherwise be difficult to treat is desirable as is the portable nature of the device. Further research including larger patient numbers with increased follow-up is required for a device that I am confident will be a useful addition to our treatment armamentarium for the treatment of BE with dysplasia.	assessment of the evidence on the efficacy and safety of that individual interventional procedure and it does not evaluate comparative effectiveness of different procedures for the same indication.

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