Endoscopic ablation of dysplastic Barrett's oesophagus comparing argon plasma coagulation and photodynamic therapy: a randomized prospective trial assessing efficacy and cost-effectiveness


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared two techniques of endoscopic mucosal ablation to treat dysplastic Barrett's oesophagus (BO). The techniques were argon plasma coagulation (APC), a non-contact electrocoagulation procedure used in flexible endoscopy, and photodynamic therapy (PDT), a non-thermal chemical process. APC was performed in an outpatient setting in an endoscopy unit, at a power setting of 65 W and with an argon gas flow of 1.8 L/minute, in 1 to 6 sessions. PDT was performed in a gastroenterology ward 48 hours after intravenous injection of Photofrin 2 mg/kg, using 630-nm red laser light with 200 J/cm delivered through a PDT balloon in 1 session. All patients received treatment with high-dose proton-pump inhibitors.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients of either gender with circumferential BO of at least 3 cm and low-grade dysplasia (LGD), or high-grade dysplasia (HGD) with histological diagnosis confirmed by biopsy performed no more than 3 months before study entry. The exclusion criteria included patients known to have oesophageal malignancy of any form, prior oesophageal resection, prior mucosal ablative therapy of endoscopic mucosal resection, patients with predominantly tongues rather than circumferential Barrett's, and patients known to have porphyria. Further exclusion criteria were women pregnant or trying to get pregnant, patients not using contraception, and patients intolerant to endoscopy.

Setting
The setting was tertiary care. The economic study was carried out at the University Hospital Aintree, Liverpool, UK.

Dates to which data relate
The dates to which the effectiveness evidence and resource use data referred were not reported. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same population sample as that used in the effectiveness study.

**Study sample**
The patients were identified from endoscopy and histopathology hospital records. Patients with significant co-morbidities were excluded, as were patients who opted to have APC. A computer-generated randomisation process was used to allocate the enrolled patients in each arm. Sample size and power calculations were reported. These found that 32 patients (16 in each arm) would be needed to achieve significance at the 5% level with 90% power. Twenty-six of the 32 patients identified from hospital records were randomised into two groups of 13 patients. Three patients with significant co-morbidities were excluded, while 3 patients opted to have APC and were not included in the randomisation process. In the APC group, 11 patients were male (84.6%), the median age was 58 years, the median length of BO was 5 cm, 12 patients had LGD, and 1 patient had HGD. In the PDT group, 10 patients were male (76.9%), the median age was 65 years, the median length of BO was 5 cm, 11 patients had LGD, and 2 patients had HGD.

**Study design**
The study was a single-centre, prospective, randomised clinical trial with two follow-up assessments at 4 and 12 months. Blinding of the outcome assessment and randomisation concealment were not reported. In the APC group, 3 patients with LGD were lost to follow up and 1 patient with HGD, which was eradicated, was deemed unfit for further follow-up endoscopy. These patients were excluded from the 12-month follow-up data analysis.

**Analysis of effectiveness**
The data were analysed on the basis of treatment completers only. The primary outcomes assessed were Barrett's length eradication and dysplasia eradication. Adverse effects were also analysed and reported. The chi-squared test with Yates' correction for continuity was used to analyse the mucosal ablation data. There were no significant differences in demographic and clinical characteristics between the groups at baseline.

**Effectiveness results**
At the 4-month follow-up, the median length of BO eradicated was 3 cm (65%) with APC and 3 cm (57%) with PDT. The corresponding figures at the 12-month follow-up were 2.5 cm (56%) with APC and 3 cm (60%) with PDT. There was no statistical difference between the two groups in length of BO eradicated at 4 months.

At the 4-month follow-up, 8 (62%) patients in the APC group and 10 (77%) in the PDT group had their dysplasia eradicated. The PDT group had significantly more dysplasia eradicated compared with the APC group (95% confidence interval, CI: 0.66 - 0.096; p=0.03).

At the 12-month follow-up, 6 (67%) patients in the APC group and 10 (77%) in the PDT group had their dysplasia eradicated.

The response to treatment in the two groups was maintained at the 12-month follow-up.

Three (23%) patients in the APC group and 4 (31%) in the PDT group developed severe side effects.

**Clinical conclusions**
PDT and APC were similarly effective in eradicating Barrett's mucosa. However, PDT was more effective in eradicating dysplasia within the Barrett's segment.

**Measure of benefits used in the economic analysis**
The outcome measure used in the economic analysis of the two procedures was the difference in mean effects for percentage Barrett's eradication and for dysplasia eradication at 4 and 12 months in both cases. These measures were
Direct costs
The direct costs included were the costs of endoscopy, accessories and drugs directly related to endoscopic procedures, and hospital bed costs either as part of the treatment or as a result of adverse effects. The cost of APC included the costs of endoscopy and the fibre. The cost of PDT included the costs of endoscopy, photosensitiser, photofrin, laser fibre, PDT balloon and hospitalisation. The costs for an extra session of endoscopy for stricture dilatation were also included. The authors used charges taken from the University Hospital Aintree NHS Trustee as a proxy for costs. Discounting was not carried out since the costs were not incurred over more than 2 years. The quantities and the costs were not analysed separately, although detailed treatment protocols were reported. The quantities and the costs were estimated on the basis of actual data. The price year was not reported.

Statistical analysis of costs
The costs seem to have been treated stochastically. No statistical tests were reported.

Indirect Costs
No indirect costs were reported.

Currency
UK pounds sterling (£).

Sensitivity analysis
The authors stated that a sensitivity analysis, based on the 95% CIs for both costs and effects, was undertaken.

Estimated benefits used in the economic analysis
At 4 months, the difference in mean effect for percentage Barrett's eradication between the two procedures was 65% for APC and 57% for PDT, that is, a net change of 8%. At 12 months, the difference was 56% for APC and 61% for PDT, a net change of 5%.

For dysplasia eradication, at 4 months there was a difference of 2 patients between the two procedures, with 10 patients in the PDT group and 8 in the APC group. At 12 months, 6 out of 9 patients were eradicated in the APC group compared with 10 out of 13 patients in the PDT group, a difference of 10%.

Cost results
The cost per patient was 1,341 for APC and 2,804 for PDT. The difference in mean costs between the two procedures was 1,463.

Synthesis of costs and benefits
The costs and benefits were summarised in the form of an incremental cost-effectiveness ratio (ICER), by dividing the total costs by the percentage difference in Barrett's eradication or dysplasia eradication.

For percentage Barrett's eradication at 4 months, APC was the dominant strategy in that it was both less expensive (1,341 versus 2,804) and more effective (65% versus 57%). At 12 months, the ICER was 266, that is, it would cost an additional 266 for every percentage reduction in Barrett's using PDT.

In the sensitivity analysis, the ICER ranged from 125 to situations where APC was dominant.
For dysplasia eradication at 4 months, it would cost an additional 732 per patient eradicated. At 12 months, the additional cost would be 146 per percentage difference in eradicated patients using PDT.

**Authors' conclusions**
Although photodynamic therapy (PDT) and argon plasma coagulation (APC) were similarly effective in eradicating Barrett's mucosa, PDT was more effective in eradicating dysplasia within the Barrett's segment but at an extra cost. The occurrence of buried columnar glands and carcinoma warrants caution. Whether it is worth incurring the extra cost depends on the benefits of dysplasia eradication and cancer prevention.

**CRD COMMENTARY - Selection of comparators**
The authors justified their choice of the comparators, stating that recent data suggested that early and appropriate endoscopic interventions with ablative techniques may lead to a better prognosis. You should judge whether these ablative techniques are relevant in your setting, or whether other comparators from other techniques or combinations of them could also have been relevant.

**Validity of estimate of measure of effectiveness**
The analysis was based on a prospective randomised clinical trial, which was adequate for the study question. The study sample was representative of the study population. A power calculation and significance level were given. However, since the final sample size was smaller (n=26) than that required by the power calculation (n=32), the study may have had insufficient power to detect statistical significance in BO eradication. The patient groups were shown to be comparable at analysis. Nevertheless, blinding of the outcome assessment and randomisation concealment were not reported, which may introduce potential bias.

**Validity of estimate of measure of benefit**
The estimation of benefits was obtained directly from the effectiveness analysis. This choice of analysis was justified. The measure used (incremental cost per percentage reduction) could be useful in this case, but it limits the comparability to other economic evaluations in other health fields.

**Validity of estimate of costs**
The analysis of the costs was performed from the perspective of a single provider and charges were used as a proxy of costs. The use of charges to proxy costs has the limitation of not reflecting true opportunity costs, thus restricting the external validity of the results. All relevant cost categories were reported since the authors provided very detailed treatment protocols. However, the costs and the quantities were not reported separately, which does not enable the analysis to be easily extrapolated to other settings. The costs were treated stochastically. A statistical analysis of the costs was not reported, although sensitivity analyses of cost-effectiveness were conducted. The price year was not reported, which will not aid future reflation exercises. Discounting was not necessary since the study had a very short-term time horizon.

**Other issues**
The authors compared their results with other studies, finding them to be comparable with those of studies using single ablative techniques. The issue of generalisability to other settings was not addressed. The study referred to patients with dysplastic BO and this was reflected in the authors' conclusions. The authors did not present their results selectively and their conclusions reflected the scope of the analysis. However, the authors recognised that it was unclear why PDT was more effective than APC in eradicating dysplasia, whereas the Barrett's length eradication did not differ. One explanation provided was that the photosensitiser porfimer sodium preferentially accumulates in the dysplastic areas, resulting in selective destruction of dysplastic tissue. Thus, the effect of PDT might be more than just physical tissue ablation and, therefore, it might be more than just an endoscopic treatment. The authors did not report any further limitations.
Implications of the study
This study is the first prospective, randomised, clinical trial comparing the efficacy and the cost-effectiveness of two different endoscopic ablative techniques in patients with dysplastic BO. Further research is needed to identify the ideal ablative technique, hence these interventions cannot be recommended yet for routine clinical application. The authors stated that it would be worthwhile to explore the multimodality endoluminal therapy in future clinical trials, since combined modality treatment employing endoscopic mucosal resection techniques have shown better results. Also, they stated that long-term follow-up is needed to assess cancer prevention and the durability of the neosquamous epithelium to justify these interventions. In addition, the authors suggested that it may be possible to avoid some PDT costs (post-PDT hospitalisation) if better patient education and counselling were provided, but only long-term follow-up will be able to confirm this.

Source of funding
Funded by Axcan Pharma-Canada, Cook UK and Wyeth Pharmaceuticals UK.

Bibliographic details

PubMedID
16118910

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Age Factors; Aged; Argon /therapeutic use; Barrett Esophagus /drug therapy /mortality /pathology /surgery; Biopsy, Needle; Catheter Ablation /economics /methods; Cost-Benefit Analysis; Esophagoscopy /methods; Female; Humans; Immunohistochemistry; Laser Coagulation /economics /methods; Male; Middle Aged; Neoplasm Staging; Photochemotherapy /economics /methods; Probability; Prognosis; Prospective Studies; Reference Values; Risk Assessment; Sensitivity and Specificity; Sex Factors; Survival Rate; Treatment Outcome

AccessionNumber
22005001205

Date bibliographic record published
31/05/2006

Date abstract record published
31/05/2006