Original Article

Changes in gastric perfusion during oesophagectomy using real time laser doppler imaging may predict patients at risk of anastomotic complications

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Background: Anastomotic complications resulting from inadequate perfusion of a gastric conduit have significant implications for patient undergoing esophagectomy. The primary aim of this study was to assess the feasibility and reliability of real time laser doppler imaging (LDI) to measure changes in gastric perfusion during oesophagectomy. The secondary aim was to assess whether there were differences in perfusion between patients with and without anastomotic complications.

Methods: Using real time LDI, regional changes in perfusion were measured during construction of a gastric conduit in 20 patients undergoing oesophagectomy (14 male, 6 female, mean age 67, range 47–77 years).

Results: There was a significant fall in perfusion for the whole stomach from 93.7% to 69.9% (P<0.001) during formation of the gastric conduit within the abdomen. There were marked regional differences within the stomach with the most significant reduction in perfusion at the fundus/tip of the conduit (54.4%), although perfusion fell significantly at all regions. Of note there was a stepwise degradation in perfusion as each named artery (or major branches thereof) was ligated. There was a further significant fall in perfusion at the fundus of 10.2% to 44.2% (P<0.001) after pull through of the conduit into the thorax or neck. There was a significant difference in perfusion at the tip of the gastric conduit in those patients suffering an anastomotic complication (Leak or stricture) compared to those without (28.5% *vs.* 52.6%, P<0.001). Perfusion was significantly lower in those patients who developed an anastomotic leak (25.0% *vs.* 49.0%, P<0.01) and the gradient of this fall was steeper after ligation of the left gastric artery when compared to patients without this complication.

Conclusions: Real time non-invasive LDI provides valid and reliable measurements of gastric perfusion during oesophagectomy and could help identify patients at risk of anastomotic complications.

Keywords: Esophagectomy; esophageal cancer; perfusion; anastomosis; leak

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Introduction

Oesophagectomy necessitates the formation of a conduit to restore continuity of the upper gastro-intestinal tract. Formation of a gastric conduit is the favoured technique due to its abundant arterial supply and extensive submucosal plexus as well as the relative ease of access, preparation of the stomach and ease of transposition into the thoracic cavity with only a single anastomosis required. The gastric conduit is dependent upon the right gastro-epiploic artery to maintain adequate perfusion and ensure anastomotic healing Thomas (1). Perfusion of the proximal 20% of the gastric tube is dependent on an extensive submucosal network of capillaries (2). The overall anastomotic leak rate for patients undergoing oesophagectomy for cancer ranges from 5–24% (3,4) in different series. Anastomotic leak and stricture are associated with poorer outcomes after oesophagectomy. Those patients who suffer a leak are at particular risk of postoperative complications and reoperation. National UK data demonstrates a higher mortality rate in this group (12.1% *vs.* 1.9%) (3). Anastomotic complications are associated with poorer long term quality of life and reduced oncological survival (5). The incidence of leak after oesophagectomy has fallen over the past two decades with advances in surgical technique and perioperative care. The aetiology of anastomotic complications is multifactorial but adequate perfusion of the conduit is essential for healing of the anastomosis without complication.

Single point and scanning laser doppler flowmetry (LDF) are non-invasive techniques which have been used to measure perfusion in human tissues including the gastrointestinal tract (6-9). They utilise the Doppler principle to provide an estimate of tissue perfusion. LDF has been used to assess gastric blood flow during oesophagectomy in several studies (10-12). However technological constraints have hindered the widespread use of such devices which are both cumbersome and slow in data capture. Historically such devices are time consuming to use, require contact with the tissue being studied, measure a very small region of interest (ROI), and measurements are not reproducible when removed/reattached. They are therefore susceptible to regional variations in perfusion, as well as intra and inter-observer variation. The application of near infrared fluorescence angiography using indocyanine green has also shown promise in the dynamic assessment of gastric perfusion during oesophagectomy (13).

A new device utilising the principles of laser doppler imaging (LDI) has been developed for use in the assessment of burn depth (14,15) and has subsequently been demonstrated to provide reliable information in reconstructive surgery with tissue flaps such as breast reconstruction. The device can provide information over a much larger surface area in real time (up to 7×7 cm^2 with 140 µm pixel resolution at rate of 12/sec) providing colour images with perfusion mapping thus removing many of the difficulties of previous devices. A range of surface areas of measurement can be selected depending on the surface area and contours of the tissue of the ROI. The device measures perfusion on a device specific perfusion scale which is then converted to a percentage scale for ease of reference (*Figure 1*).

The primary objective of the study was to assess the validity and reliability of real time LDI to measure changes in gastric perfusion during oesophagectomy. A secondary objective was to assess whether there are significant differences in perfusion measurements between patients who develop anastomotic complications (leak and/or stricture) compared to patients who do not develop anastomotic complications. Ethical approval was granted by a research ethics committee of the NHS Health Research Authority. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/aoe-20-39).

Methods

A total of 20 patients undergoing oesophagectomy for cancer were included in a 12-month period from a total of 71 resections (14 male, 6 female; mean age 67; range 47–77 years). Surgery was performed by two surgeons at a single specialist Upper GI unit of a large London Teaching Hospital. Further baseline and operative characteristics of the patients are displayed in *Table 1*. Baseline demographic and perioperative data are described as means with ranges. Three different approaches were performed depending on the site and stage of the tumour. All patients received systemic neoadjuvant chemotherapy. Pre-operative haemoglobin, intraoperative mean arterial pressure and administration of vasoactive agents were recorded. Patients followed a standardised enhanced recovery after surgery protocol and underwent routine radiological assessment of the anastomosis on the fourth or fifth postoperative day. An anastomotic leak was identified on clinical and/or radiological features. Patients underwent standard post-operative follow up and an anastomotic stricture was diagnosed on a symptomatic basis in those requiring endoscopic dilatation within 3 months of surgery. Perfusion data is described as means with 95% confidence intervals. Statistical analysis was performed using the Wilcoxon signed rank test for differences in means within the study group. The Friedman test was used for differences on repeated measures within the same sample with post hoc analysis using the Wilcoxon test. For comparison of perfusion between patients with and without anastomotic

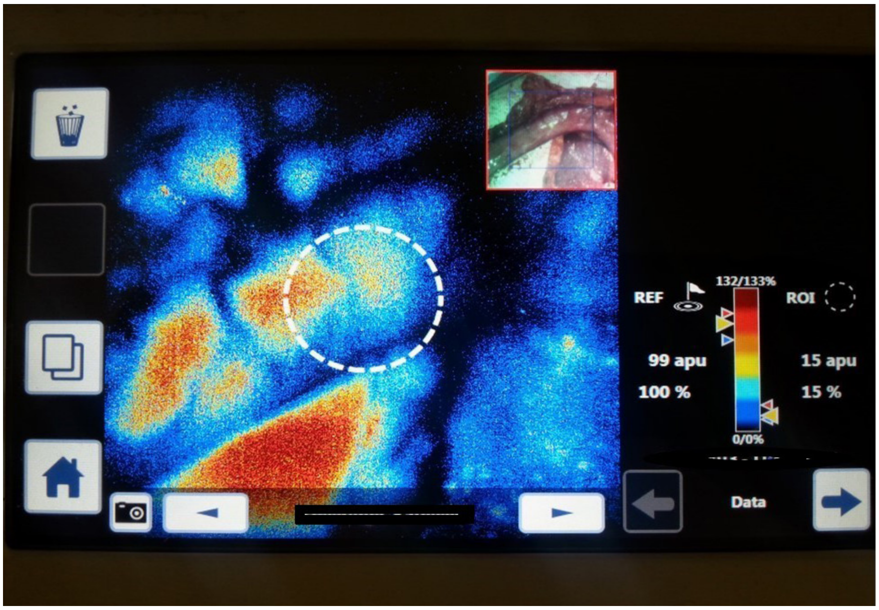

Figure 1 Real time LDI user interface showing colour perfusion map of a gastric conduit with video image (Inset top right) of the conduit lying within the laparotomy incision. The broken white circle in the main images the 2 cm pre-selected ROI in which perfusion is being measured. The colour perfusion scale in situated to the right with measurements in perfusion units (APU) and percentage of the baseline reference (REF). The perfusion scale shows markers for the mean (yellow), maximum (red) and minimum (blue) measurements reflecting changes in pressure in the microcirculation. LDI, laser doppler imaging; ROI, region of interest.

complications Mann-Whitney U was used for comparison of means and Kruskal-Wallis tests for comparison on repeated measures. Results are expressed as mean values with 95% confidence intervals unless otherwise stated. Results are expressed using conventional and accepted levels of significance. Analysis was undertaken using the SPSS statistical software package (SPSS Statistics v.22, IBM, New York, US). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the research ethics committee of the NHS Health Research Authority (REC reference: 15/NI/0087) and informed consent was taken from all the patients.

Technique

During surgery, sterility of the operative field was preserved by placing the scanner head of the device in a transparent sterile drape. Its design on a modular arm is such that contact was avoided when positioned over the patient. The device head was positioned over the patient at a distance at which two green lasers projected onto the stomach were united at a single point which determined the correct focal length for accurate measurements. A 2-cm diameter ROI was selected and measurements of 5 seconds in duration were taken allowing for temporal variation in perfusion recordings. Values obtained were a mean of perfusion during these 5 second periods. Measurements were performed between 2 and 4 minutes after ligation of each vascular pedicle. Calibration and measurements were performed by a single surgeon for all subjects.

At operation, baseline measurements were performed prior to gastric mobilisation. Three ROIs on the anterior surface of the stomach—the gastric antrum, mid body and fundus—were selected. The device was calibrated to a baseline at the antrum between 2–3 cm from the pylorus in the region closely apposed to the right gastro-epiploic artery on which the perfusion of the future conduit is dependent. Sequential measurements were taken from each ROI following ligation and division of each named vascular. Dissection and ligation of vascular pedicles was performed with ultrasonic dissection or suture ligation as indicated. A standard gastric conduit was constructed using a linear stapling device. Further measurements were then taken from the conduit within the abdominal cavity and from the distal tip of the conduit (region of the fundus) in the thoracic cavity or neck before and after construction of an

Table 1 Summary of patient and procedural characteristics

Variable	Values
Age (years)	67 [47–77]
Gender	14 M, 6 F
ASA grade	
ASA 1	1
ASA 2	18
ASA 3	1
Haemoglobin (g/L)	118.75 [92–137]
Histological type	
SCC	3
ACA	17
Operation	
Transhiatal	10
Left thoracoabdominal	6
3 stage	4
Stage*	
2A	1
2B	4
3A	9
3B	5
3C	1
Anastomotic complication	
Leak	4
Stricture	7 (developed in 4 with leak)

*, stage = TNM 8 (16). ASA, American society of Anaesthesiologists; SCC, squamous cell carcinoma; ACA, adenocarcinoma.

oesophagogastric anastomosis.

Results

There was no significant difference in preoperative haemoglobin concentration, blood loss or mean arterial pressure (P>0.05) between the participants and no patient required intraoperative inotropic support. Of the 20 patients included in the study, 7 developed an anastomotic complication of whom 4 had an anastomotic leak and subsequent stricture and 3 developed a stricture only. A total of 71 patients underwent oesophagectomy at the authors' institution in the year of study of whom 6 developed an anastomotic leak. The patients with a leak were managed non-operatively and there were no in hospital deaths. The patients with an anastomotic stricture underwent balloon dilatation within 3 months of surgery. There were no significant differences in the baseline characteristics of patients with and without complications for age, gender, ASA grade, haemoglobin concentration, mean arterial pressure or clinical stage (P>0.05).

Table 2 Mean change in perfusion during conduit formation—by region of interest compared to baseline measurement—expressed as percentage of baseline with 95% CI where baseline =100%

	Conduit (95% CI)	Sig. (P)
ROI		
Stomach (mean of all ROIs)	69.9% (63.0–76.8%)	<0.001
Antrum	83.1% (74.5–91.7%)	<0.01
Body	72.3% (61.3–83.2%)	<0.01
Fundus	54.40% (45.0–63.8%)	<0.001
Conduit tip		
Pre-anastomosis	44.2% (37.5–50.9%)	<0.001
Post-anastomosis	45.4% (38.8–51.9%)	<0.001

ROI, region of interest; Baseline, before gastric mobilisation; Conduit, after formation of gastric conduit in abdomen; Conduit tip, tip of conduit immediately before and after anastomosis in neck or thorax.

There was a significant fall in perfusion for the whole stomach from 93.5% (89.3–98.0%) to 69.9% (63.0–76.8%, P<0.001) during formation of the gastric conduit within the abdomen. The fall in perfusion was most marked at the distal tip of the conduit (54.4%, 45.0–63.8%, P<0.001), although perfusion fell significantly at all ROIs. Of note there was a stepwise degradation in perfusion as each named artery (or major branches thereof) was ligated. There was a further significant fall in perfusion at the fundus of 10.2% to 44.2% (37.5–51.1%, P<0.001) after pull through of the conduit into the thorax or neck. Results are displayed in *Table 2* and *Figure 2*.

A stepwise degradation in perfusion was observed during ligation of each vascular pedicles known to contribute to gastric perfusion and this was significant at the conduit tip as each pedicle was ligated (*Figure 3*). In the body this trend was again noted but was significant after ligation of the left gastric artery. In the antrum the overall fall in perfusion from baseline to conduit formation was significant but the

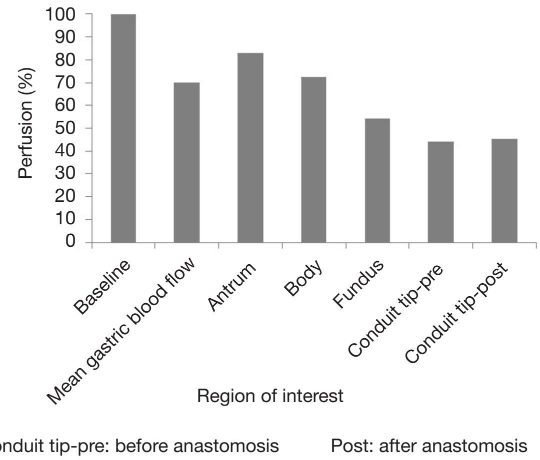

Figure 2 Change in perfusion during conduit formation.

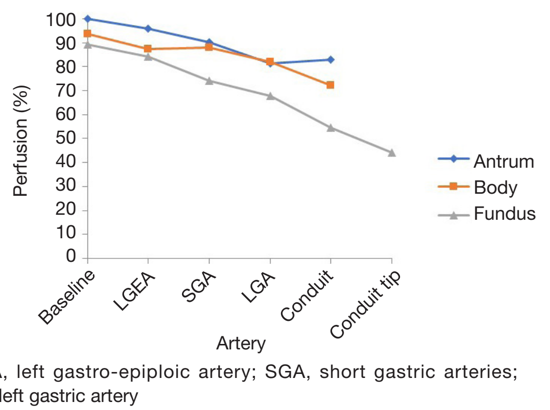

Figure 3 Change in perfusion at each region of interest during sequential ligation of named arteries and subsequent conduit construction.

relative cumulative impact of ligation of each pedicle did not reach significance.

There were significant differences in perfusion measurements between patients with and without anastomotic complications. For all patients irrespective of complications a fall in perfusion was observed after transposition of the conduit into the posterior mediastinum. For patients with any anastomotic complication (leak or stricture) regional perfusion was lower at the tip of the conduit after construction in the abdomen and after transposition of the conduit into the neck or thorax, before and after construction of an oesophagogastric anastomosis (*Table 3*).

For patients with an anastomotic leak perfusion was significantly lower at the conduit tip at all stages during formation of an anastomosis when compared to those without leak (pre anastomosis—25.0, 95% CI: 5.51–44.49, P<0.01). A significant difference in fall in perfusion after transposition into the mediastinum was again noted.

A similar trend was observed when comparing patients with an anastomotic stricture to those without. However perfusion remained slightly higher relative to patients with a leak. Although perfusion was lower at the tip of the conduit before transposition in the stricture group when compared to those without this did not reach statistical significance until after transposition of the conduit into the mediastinum (28.57, 95% CI: 18.8–38.33, P<0.001).

When comparing patients without complication to those with an anastomotic leak a significant difference in perfusion at the gastric fundus and tip of the conduit was noted during ligation of arteries. This difference was significant after ligation of the left gastric artery (*Figure 4*).

Conclusions

The results of the study support the validity and reliability of the device and suggest that it is capable of identifying patients at risk of anastomotic complications. In addition it appears to show a stepwise fall in gastric perfusion during sequential ligation of named vascular pedicles and a further fall with transposition of the conduit into the chest or neck.

In experimental conditions laser doppler flow techniques have been used to estimate changes in perfusion during oesophagectomy (10-12,17). As in other anatomical locations doppler assessment of perfusion has been validated against existing measures of perfusion but there is no gold standard (18-20). Earlier studies using single point LDF had provided some indication of the regional changes in perfusion that occur during conduit formation (12). In the small number of studies utilising LDF principles during conduit formation mean gastric blood flow fell by 40–60% with more substantial reduction in perfusion noted at the fundus of the stomach or anastomotic site (25–45%) (10-12,21). The measurements of perfusion recorded in this study demonstrate a range of values which are consistent with previous studies supporting the reliability and validity of the device in this clinical application. The current technique has overcome some of the difficulties encountered with similar technologies. Firstly, both the speed of image acquisition and area of measurement have been increased without compromising the accuracy of results. Secondly, the relative portability, mobility and simplicity of the user

Table 3 Changes in perfusion at the tip of the gastric conduit after construction and anastomosis

ROI	No complication	Any complication	P	Leak	P	Stricture	P
Conduit tip after construction	58.69 (48.51–68.86)	37.25 (12.21–62.29)	<0.05	37.25 (12.21–62.29)	<0.05	45.86 (26.77–64.95)	0.165
Conduit tip after pull up	49.00 (43.50 -54.50)	25.0 (5.51–44.49)	<0.01	25.0 (5.51–44.49)	<0.01	28.57 (18.8–38.33)	<0.001
Conduit after anastomosis	50.38 (46.07–54.68)	25.25 (1.00–49.50)	<0.01	25.25 (1.00–49.50)	<0.01	33.57 (19.69–47.50)	<0.005

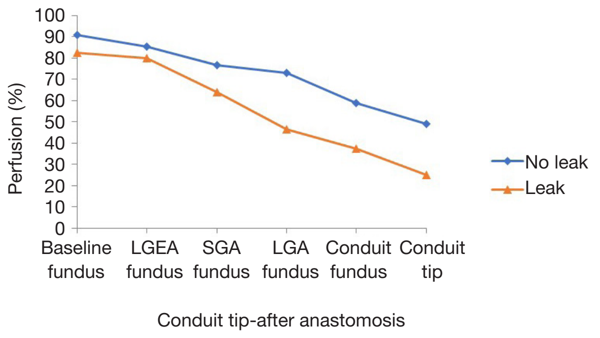

Figure 4 Change in gastric perfusion at the fundus/conduit tip after ligation of named arteries—no leak *vs.* leak. LGEA, left gastro-epiploic artery; SGA, short gastric arteries; LGA, left gastric artery.

interface within a single image capture and processing unit has improved the clinical acceptability and utility of the technique.

The results of this study have shown significant regional differences in perfusion for all subjects. Perfusion at the fundus, or tip of the conduit, was most reduced during conduit formation and was significantly lower in patients who developed an anastomotic complication. Of interest is the observation that perfusion was markedly reduced after transposition of the conduit in to the mediastinum. This could be the result of anastomotic tension, constriction at the hiatus or torsion of the conduit resulting in further compromise to the most distal and poorly perfused region of the conduit which is dependent on a submucosal network of small arterioles (2,22).

In addition a stepwise reduction in perfusion was observed as individual vascular pedicles were ligated. This change was most marked at the fundus, was significantly lower in those patients who developed an anastomotic leak and appeared most marked after ligation of the left gastric artery. This may be a result of the cumulative effect of ligation of vascular pedicles on total gastric flow or possibly indicates the importance of the individual contribution of the left gastric artery to total and regional perfusion. A similar trend in perfusion measurements at all stages was noted for patients who developed an anastomotic stricture. In this group, perfusion remained higher at each step when compared to the leak group, suggesting that stricture and leak exist on a continuum of poorer perfusion, the size of which determines the severity of the anastomotic complication.

Identification of variations in local perfusion within the stomach during oesophagectomy could alert the surgeon to the potential risks of a poorly selected site for oesophagogastric anastomosis. Selection of a relatively well perfused site on the stomach for anastomosis avoiding the tip of the conduit where possible could help reduce the risk of complications. This is of greater concern when constructing a cervical anastomosis where a longer conduit is required and the anastomosis is likely to be closer to the tip of the conduit, the area most vulnerable to ischaemia. Where poor perfusion is demonstrated further operative manoeuvres such as division of the right gastric pedicle, mobilisation of the hepatic flexure and Kocherisation of the duodenum and can further lengthen the conduit permitting a more proximal site for anastomosis.

In this study all patients had received neoadjuvant chemotherapy prior to surgery. In many centres where the standard pathway includes neoadjuvant chemoradiotherapy there have been concerns regarding an increased risk of anastomotic complications and this risk may increase in a dose dependent manner in relation to the gastric fundus (23). However in several studies no clear evidence of an increased risk has been demonstrated (24,25).

Several small experimental studies using different intraoperative techniques for perfusion monitoring have attempted to demonstrate an association between poor perfusion and anastomotic complications. Techniques such as laser speckle contrast imaging, gastric tonometry, Doppler flowmetry, angiography and optical fibre spectroscopy (26-28) have been assessed and the authors have concluded that these techniques could influence intraoperative decision making. However the techniques have failed to gain wider acceptance due to issues of technical feasibility and reproducibility. A recent meta-analysis of small non-randomised trials suggested that there may be a benefit from the use of intraoperative indocyanine green in selection of anastomotic site (13). A systematic review of near infrared fluorescence angiography with indocyanine green concluded that this technique is feasible and may be useful in predicting outcome in terms of anastomotic leak (29). This technique may also have potential in terms of oncological resection margins and lymphadenectomy in both open and laparoscopic approaches (30). Laser Doppler principles are more difficult to apply to minimally invasive approaches and would therefore limit the application of real time LDI in its current form.

The use of goal directed fluid therapy has been assessed in an attempt to maintain perfusion pressure and reduce episodes of hypo-perfusion in the human gastric mucosa and gastric conduit microcirculation in animal models but with variable results (31-33). Various pharmacological agents have also been shown to affect splanchnic and local tissue micro-perfusion. Epidural anaesthesia induces a degree of systemic hypotension resulting in gastric conduit hypo-perfusion which can be countered with adrenaline (34-36). However, the effect of positively inotropic and vasodilating agents have yielded conflicting results in the maintenance of gastric microperfusion (37-40). The increasing use of minimally invasive/hybrid techniques has negated the use of epidural anaesthesia in many cases. In physiological terms careful use of adjuncts which optimise oxygen delivery to the splanchnic tissues and sustain optimal gastric micro-perfusion could all help to reduce the risk of hypo-perfusion of the conduit and ischaemia at the anastomosis. A recent review of standardized protocols for perioperative fluid therapy and goal directed therapy found that there was a lack of evidence to support such protocols. However at the authors' centre the implementation of such protocols within the context of an ERAS programme was considered beneficial in terms of risk of anastomotic complications and outcome (41). The impact of ischaemic preconditioning of the stomach prior to oesophagectomy has been the focus of intense interest (42). However overall results are mixed and a recent small randomised trial did not demonstrate a benefit in perfusion as measured by LDF (43). It is likely that many of the improvements in operative outcome in this group of patients witnessed over the past 20 years are due to a greater awareness of, and response to, the local and systemic pathophysiological consequences of poor perfusion in the perioperative period. The application of LDI may be a valuable tool in assessing perfusion of the gastric conduit alerting the operating surgeon to potentially vulnerable sites at the tip of the conduit thereby reducing the risk of anastomotic complications. It has in this study provided a valuable insight in to the changes in perfusion in the stomach during oesophagectomy.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/aoe-20-39

Data Sharing Statement: Available at http://dx.doi.org/10.21037/aoe-20-39

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aoe-20-39). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the research ethics committee of the NHS Health Research Authority (REC reference: 15/NI/0087) and informed consent was taken from all the patients.

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