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Is Radiofrequency Ablation Effective In Treating Barrett's Esophagus Patients with High-Grade Dysplasia?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies

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ABSTRACT

Objective: The objective of the selective EBM review is to determine whether or not “Is radiofrequency ablation effective in treating Barrett’s esophagus patients with high-grade dysplasia?”

Study Design: Review of two randomized controlled trials and one cohort study. All three studies were published in English in peer-reviewed journals after 2000.

Data Sources: Two randomized controlled trials and one cohort study found via PubMed.

Outcome(s) Measured: All three studies measured eradication of dysplasia via biopsy evaluation. Other outcomes measured included progression to high-grade dysplasia or adenocarcinoma based on histology findings, overall cancer risk based on observations of patients in the registry, and rate of serious adverse events determined by any event that led to death or required hospitalization.

Results: Phoa et. al and Haidry et. al found that RFA treatment was successful in treating dysplastic Barrett’s esophagus. Though Shaheen et. al found that RFA treatment was successful in eradication of dysplasia, given the poor study design and lack of control group, it cannot be concluded whether or not RFA treatment was successful for patients with high-grade dysplasia.

Conclusions: Based on the results of the Haidry and Phoa studies, RFA was shown to be an successful and cost-effective treatment method for the eradication of dysplastic Barrett’s esophagus. The Shaheen study found that RFA was effective, however it is difficult to assess validity of the data due to lack of a control group throughout the entirety of the study.

Key Words: Barrett’s esophagus, radiofrequency ablation, dysplasia

INTRODUCTION

Barrett's esophagus (BE) is "the replacement of normal esophageal squamous mucosa by specialized intestinal columnar mucosa," a complication of longstanding gastroesophageal reflux disease (GERD) that is seen in about 10 to 15% of patients, increasing patients' risk of developing esophageal adenocarcinoma.^{4,10} Some patients with Barrett's esophagus may develop dysplasia, a precancerous change in the lining of the esophagus - though risk of developing cancer is low at just "0.5 percent per year."¹⁰ This paper evaluates two randomized controlled trials (RCTs) and one cohort study evaluating the efficacy of radiofrequency ablation (RFA) as a method of eradicating high-grade dysplasia in patients with Barrett's esophagus.

The prevalence of Barrett's esophagus is about 1.6% of the general population.⁸ In the United States, adenocarcinoma of the esophagus is becoming more prevalent and is most often seen in obese, Caucasian males, with a history of GERD.¹⁰ Though both photodynamic therapy (PDT) and RFA are successful in treating dysplastic BE, success rates of eradication are higher with RFA and "five times less costly than PDT."¹ RFA treatment course involves 2 to 3 sessions 1 to 4 times per year, with an average of 2 to 4 days of missed work per session. Given its short recovery time, it is a cost-effective option for the treatment of dysplasia.⁵

Though the exact cause of Barrett's esophagus is unknown, history of longstanding GERD increases the risk of developing the condition.¹⁰ When a patient is diagnosed with Barrett's esophagus, a periodic endoscopy is the next step in management of this condition. If the endoscopy does not show evidence of dysplasia, it should be repeated approximately every three years.¹⁰ Typically first line treatment begins with high dose proton pump inhibitors or histamine blockers.⁹ For high-grade dysplasia or cancer, esophagectomy is an option.²

Once Barrett's esophagus progresses to some form of dysplasia, more serious measures must be taken to prevent further advancement to adenocarcinoma of the esophagus. One such measure is RFA, which compared to PDT has a smaller side effect profile and costs less. In addition, RFA can be controlled to a specified depth.¹

OBJECTIVE

The objective of this selective EBM review is to determine whether or not “Is radiofrequency ablation effective in treating Barrett's esophagus patients with high-grade dysplasia?”

METHODS

This review focuses on patients over the age of 18 with Barrett's esophagus and endoscopic evidence of dysplasia, where all studies focus on RFA as the primary intervention. Shaheen et. al focus on RFA compared to a sham endoscopic procedure.⁷ Haidry et. al focus on RFA and endoscopic mucosal resection in a cohort study.³ Phoa et. al focus on RFA compared to endoscopic surveillance (high-resolution endoscopy).⁶ Many outcomes are measured including progression to high-grade dysplasia or adenocarcinoma, eradication of dysplasia, durability of response, adverse reactions, and overall cancer risk. Two of the studies are RCTs and one is a cohort study. All articles are published in English and in peer-reviewed journals found via Pubmed using keyword searches such as “Barrett's esophagus”, “radiofrequency ablation,” and “dysplasia.” Inclusion criteria include articles published after the year 2000. Exclusion criteria include patients under the age of 18 and history of malignancy. All articles are selected based on relevance to the clinical question and inclusion of patient oriented outcomes (POEMs). Statistical analysis is reported using Cox proportion hazard models, t tests, Kaplan-Meier survival curves, χ^2 tests, Fisher's exact test, p value, NNT, and SD.^{3,6,7}

Table 1 – demographics and characteristics of included studies

| Study | Type | # Pts | Inclusion Criteria | Exclusion Criteria | W/D | Interventions |
|-----------------------------|--------|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----------------------------------------------------------|
| Haidry (2015) ³ | Cohort | 920 | Men and non-pregnant women over the age of 21 years with no contraindications to endoscopy. | Pregnant women, contraindications to endoscopy, <21 years of age. | 412 | Radiofrequency ablation and endoscopic mucosal resection |
| Phoa (2014) ⁶ | RCT | 136 | | Prior endoscopic treatment for Barrett esophagus; history of high-grade dysplasia or adenocarcinoma; active secondary malignancy; estimated life expectancy less than 2 years; age of 18 years or younger or 85 years and older. | 7 | Radiofrequency ablation |
| Shaheen (2011) ⁷ | RCT | 127 | Endoscopically evident, non-nodular, dysplastic BE \leq 8cm in length; 18-80 y/o; for subjects with HGD, additional requirement of endoscopic US negative for lymphadenopathy or esophageal wall abnormalities within 12 months of enrollment; previous EMR permissible \geq 8 weeks before entry, provided that subsequent endoscopy demonstrated non-nodular dysplasia. | Pregnancy; active esophagitis or stricture; history of esophageal malignancy, varices, uncontrolled coagulopathy, or life expectancy of <2 years, as judged by the investigator. | 10 | Radiofrequency ablation |

OUTCOMES MEASURED

Outcomes measured are those that focus on patient oriented evidence that matters (POEM). All three studies measure eradication of dysplasia via biopsy evaluation.^{3,6,7} Other outcomes measured include progression to high-grade dysplasia or adenocarcinoma based on histology findings, overall cancer risk based on observations of patients within the registry, and rate of serious adverse events determined by any event that led to death or required hospitalization.^{3,6,7}

RESULTS

This review examines two RCTs and one cohort study that evaluate RFA as a method of eradication of dysplasia in Barrett's esophagus patients. The results of the two RCTs are reported as dichotomous data, so numbers needed to treat (NNT), relative benefit increase (RBI), and absolute benefit increase (ABI) are calculated. The results from the cohort study cannot be converted to dichotomous data.

In the Shaheen study, 127 subjects were divided into either a low-grade dysplasia (LGD) or a high-grade dysplasia (HGD) group.⁷ Inclusion and exclusion criteria can be found in Table 1. Subjects were then randomized to receive either the sham endoscopic procedure (SHAM) or the RFA treatment. Subjects in the experimental group received up to 4 RFA treatments at 0, 2, 4, and 9 months based on results from the biopsies, and 1 treatment in the second year. After one year, 117 of the subjects completed follow up and 35 of the 39 subjects in the SHAM group were "eligible for cross-over to the RFA treatment."⁷ The remaining 4 participants developed esophageal adenocarcinoma and were no longer eligible for crossover treatment. In the second trial, 119 subjects underwent RFA, and 106 subjects made it to the 2-year follow up. The primary outcome measured was whether or not complete eradication of dysplasia could be

achieved. After 2 years, 51/52 (98%) subjects with low-grade dysplasia achieved complete eradication and 50/54 (95%) subjects with high-grade dysplasia achieved complete eradication.

The results from the study can be found in Table 2.

Due to the crossover treatment option after one year, there was no longer a control group at the end of the study. Therefore, values in Table 2 were calculated using the low-grade dysplasia group as the control and the high-grade dysplasia group as the experimental group. NNT was calculated to be -33, meaning for every 33 patients treated with RFA, one fewer would achieve complete eradication of high-grade dysplasia. Given the poor study design, it is difficult to assess whether or not RFA treatment was successful in eradication of high-grade dysplasia, as there was no control group at the end of the study and therefore no reported p value. Upper gastrointestinal hemorrhage and chest discomfort with nausea were the most common adverse events noted after the study. No “procedure-related” deaths occurred.⁷

Table 2. Treatment Effects

| STUDY | CER | EER | RBI | ABI | NNT |
|----------------------|------|------|--------|-------|-------|
| Shaheen ⁷ | .98 | .95 | -0.031 | -0.03 | -33 |
| Phoa ⁶ | .279 | .926 | 2.32 | .647 | 1.545 |

In the Phoa study, 140 subjects were randomized to either the experimental group, where they received RFA, or the control group, for endoscopic surveillance.⁶ Patients in the experimental group were treated with either a circumferential or a focal device based on the degree of their disease. RFA sessions were scheduled every 3 months until there was complete eradication of dysplasia. Follow up endoscopy was 3 months after the last therapy session, where biopsy samples were taken. The experimental group also received “double-dose proton pump inhibition as maintenance therapy.”⁶ Patients in the control group “underwent high-resolution endoscopy.”⁶ One subject in the RFA group progressed to adenocarcinoma and was treated with endoscopic resection. This study found that RFA treatment was successful in treating BE

dysplasia, with a statistically significant p value <0.001. Results from the study can be found in Table 3. Esophageal stricture, bleeding, mucosal laceration, and abdominal pain were the noted adverse events.⁶

Table 3. Complete Eradication of Dysplasia

| STUDY | P-VALUE | OR | 95% CI | RR |
|---------------------|-----------|-------|----------------|-----|
| Haidry ³ | P <0.0001 | 1.103 | 1.023 to 1.190 | N/A |
| Phoa ⁶ | P <0.001 | N/A | 59.4-81.6% | 90% |

In the Haidry cohort study, 920 patients within the UK registry were referred for treatment – 508 completed treatment.³ RFA was completed with either a circumferential or with several focal devices for shorter segments of Barrett’s esophagus. Patients received an average of 2 to 3 RFA treatments. At the end of protocol, patients without dysplasia were followed every 3 months for post-RFA surveillance during the first year, every 6 months for the following year, and then annually after that. From 2008-2010, 206/266 (77%) of all patients achieved complete eradication of dysplasia at the end of protocol.³ From 2011-2013, 222/242 (92%) of all patients achieved complete eradication of dysplasia at the end of protocol.³ From 2008-2010 and then from 2011-2013, 76% and 92% of patients with high-grade dysplasia (HGD) achieved complete eradication respectively.³ These results were statistically significant, as the p value was less than 0.0001. Results can be found in Table 3.

DISCUSSION

Radiofrequency ablation is an “endoscopic technique in which diseased tissue is exposed to heat energy and destroyed.”² RFA is generally used as a treatment for Barrett’s esophagus. The procedure lasts about 25-50 minutes and on average, patients have anywhere from 2 to 3.5 treatments. Commonly after treatment, patients complain about “chest discomfort, sore throat and/or painful or difficult swallowing after the procedure.”⁵ Although RFA is considered a generally safe procedure, and complications are seen in <1% of patients, there is always a

possible risk of esophageal stricture, bleeding, infection, and death.^{2,5} Eradication rates range from 72-100%.⁵

CONCLUSION

After careful review of these three studies, there is evidence in both the Phoa and Haidry studies to suggest that radiofrequency ablation is a safe and effective treatment for patients with endoscopic evidence of Barrett's esophagus with dysplasia. Future research, however, is warranted and should focus more on patients with high-grade dysplasia. Although the subjects in the Shaheen study did see improvement in their dysplasia after the RFA treatments, due to the poor study design and lack of control group at the end of the study, it is difficult to conclude whether or not RFA was an effective treatment for patients with high-grade dysplasia. Compared to other therapies, including PDT, RFA has a smaller side effect profile and costs less.¹ The studies each maintained appropriate follow up time with the subjects.

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