# Prevalence and predictors of recurrent neoplasia after ablation of Barrett's esophagus

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**Background:** The incidence and risk factors for recurrence of dysplasia after ablation of Barrett's esophagus (BE) have not been well defined.

**Objective:** To determine the rate and predictors of dysplasia/neoplasia recurrence after photodynamic therapy (PDT) in BE.

**Setting:** Retrospective analysis of a prospective cohort of BE patients seen at a specialized BE unit.

**Methods:** Patients underwent a standard protocol assessment with esophagogastroduodenoscopy and 4-quadrant biopsies every centimeter at 3-month intervals after ablation. Recurrence was defined as the appearance of any grade of dysplasia or neoplasia after 2 consecutive endoscopies without dysplasia. Entry histology, demographics, length of BE, presence and length of diaphragmatic hernia, EMR, stricture formation, nonsteroidal anti-inflammatory drug use, smoking, and the presence of nondysplastic BE or squamous epithelium were assessed for univariate associations. Time-to-recurrence analysis was done by using Cox proportional hazards regression. A multivariate model was constructed to establish independent associations with recurrence.

**Results:** A total of 363 patients underwent PDT with or without EMR. Of these, 261 patients were included in the final analysis (44 lost to follow-up, 46 had residual dysplasia, and 12 had no dysplasia at baseline). Indication for ablation was low-grade dysplasia (53 patients, 20%), high-grade dysplasia (152 patients, 58%), and intramucosal cancer (56 patients, 21%). Median follow-up was 36 months (interquartile range 18-79 months). Recurrence occurred in 45 patients. Median time to recurrence was 17 months (interquartile range 8-45 months). Significant predictors of recurrence on the multivariate model were older age (hazard ratio [HR] 1.04, $P = .029$), presence of residual nondysplastic BE (HR 2.88, $P = .012$), and a history of smoking (HR 2.68, $P = .048$).

**Limitations:** Possibility of missing prevalent dysplasia despite aggressive surveillance.

**Conclusion:** Recurrence of dysplasia/neoplasia after PDT ablation is associated with advanced age, smoking, and residual BE. (Gastrointest Endosc 2010;71:697-703.)

Barrett's esophagus (BE) is a strong risk factor for esophageal adenocarcinoma, a malignancy with the most rapidly increasing incidence in the United States.[1] The interest in ablating BE is based on the hypothesis that eliminating dysplastic epithelium can prevent progression to cancer. Over the past decade, many ablative modalities have been developed with various outcomes.[2-9] Photodynamic therapy (PDT) is one of the most widely studied ablative techniques for BE with the longest follow-up data.[10] Recently, Overholt et al[11] reported their 5-year experience of the safety and efficacy of PDT in BE with high-grade dysplasia (HGD) and showed persistent good outcomes. Dysplasia and neoplasia recurrence rates, however, were not specifically looked at in this study.

Recurrence of dysplasia after ablation of dysplastic BE with PDT has been reported in small studies with some data available on predictors of recurrence.[12-14] Given the

*Abbreviations: BE, Barrett's esophagus; BMI, body mass index; HGD, high-grade dysplasia; DH, diaphragmatic hernia; HR, hazard ratio; LGD, low-grade dysplasia; PDT, photodynamic therapy; RFA, radiofrequency ablation.*

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long follow-up available in patients treated with PDT,[10] this population is best suited for the study of recurrence rates, patterns, and predictors. Identification of possible predictors of recurrence of dysplasia and neoplasia after ablating BE may allow the development of interventions that can decrease recurrence and improve patient outcomes. We aimed in this study to define the rate and predictors of recurrence of dysplasia and neoplasia after ablation of dysplastic BE with PDT. Our cohort consisted of patients with BE who underwent ablation with PDT with or without EMR at a single tertiary care referral center (Mayo Clinic, Rochester, Minn) between 1992 and 2005.

**Capsule Summary**

**What is already known on this topic**

- Ablation in Barrett's esophagus (BE) eliminates dysplastic epithelium and may prevent progression to adenocarcinoma.

**What this study adds to our knowledge**

- In a retrospective analysis of 261 patients with BE, significant predictors of recurrence of dysplasia or neoplasia after photodynamic ablation were advanced age, smoking, and residual BE.

## METHODS

Patients treated in the Barrett's Esophagus Unit at the Mayo Clinic Rochester from 1992 to 2005 were included in this study. The study was approved by the institutional review board at Mayo Rochester. Data were abstracted from a prospective database maintained in the Barrett's Esophagus Unit.

Inclusion criteria included patients with BE and dysplasia/neoplasia who underwent PDT with or without EMR during the selected study period. We defined response to PDT as the absence of dysplasia on surveillance biopsy samples from the first 2 consecutive endoscopies, separated by 3 months, after ablation (ie, for at least 6 months after ablation). All patients underwent a standard protocol assessment with esophagogastroduodenoscopy and 4-quadrant biopsies every centimeter at 3-month intervals as part of the surveillance protocol. Patients who did not achieve regression to either BE with no dysplasia or squamous epithelium after the first PDT session were excluded from the analysis.

### Endoscopic ablation

**PDT.** PDT was done as previously described[15] by using intravenous porfimer sodium (Photofrin; Axcan Pharma, Mont-Saint-Hilaire, Quebec, Canada) at a dose of 2 mg/kg in 92% of the patients (in the remainder, hematoporphyrin derivative was used at a dose of 4 mg/kg). It was our practice between 1992 and 1998 to perform a second-look endoscopy 24 to 48 hours after PDT to check for adequacy of treatment and perform additional PDT if untreated areas were detected. This practice was discontinued in 1999 because it did not seem to increase treatment efficacy.

**EMR.** Endoscopically visible lesions underwent EMR for diagnostic purposes to determine histology. EMR was performed by initially injecting 10 mL of diluted epinephrine (1:100,000) solution into the submucosa underneath the lesion. Between 1992 and 2000, the technique used for EMR was a variceal ligation method with a Bard Six-Shooter (Bard Interventional Products, Billerica, Mass). Beginning in April 2000, EMR was performed by using a commercially available EMR kit (EMR-001; Olympus America Corp, Natick, Mass).

### Patient follow-up

All patients took twice-daily proton pump inhibitors after treatment and were enrolled in a surveillance protocol. The surveillance protocol consisted of an upper endoscopy and 4-quadrant surveillance biopsies performed every centimeter every 3 months in the first year regardless of ablation results. The interval was decreased to every 6 months if low-grade dysplasia (LGD) was detected and every 12 months if BE with no dysplasia or squamous epithelium was found. All pathology results were read by pathologists with expertise in BE-associated neoplasia.

### Outcome measure, data collection, and analysis

The primary outcome measure of this study was to determine the recurrence rate and factors predicting recurrence of dysplasia in BE patients who underwent PDT. Recurrence was defined as the appearance of dysplasia or neoplasia after 2 consecutive endoscopies without dysplasia. The interval of 2 consecutive endoscopies was chosen to minimize the possibility of prevalent dysplasia that was missed on surveillance biopsy samples post-ablation.

Medical records of patients meeting inclusion criteria were examined, and the following data were abstracted: number of PDT applications per treatment session, entry histology, age, sex, length of BE, presence and length of a diaphragmatic hernia (DH), performance of EMR for a visible lesion, stricture formation, entry body mass index (BMI), use of nonsteroidal anti-inflammatory drugs, smoking status (defined as smokers: current smoking, or smoking up to 30 days before ablation, or nonsmokers), date of response, and date of recurrence.

A DH length greater than a 2-cm cutoff was chosen in the univariate model to reduce the possibility of overcalling a DH at endoscopy. A BMI greater than 25 was included in the univariate model because our goal was to see whether simply being overweight was a risk for recurrence (overweight defined as a BMI $>25$). In the univariate model, a BE segment length greater than 3 cm was chosen because we wanted to check whether long-segment BE (long segment defined as $>3$ cm) was a risk factor for recurrence.

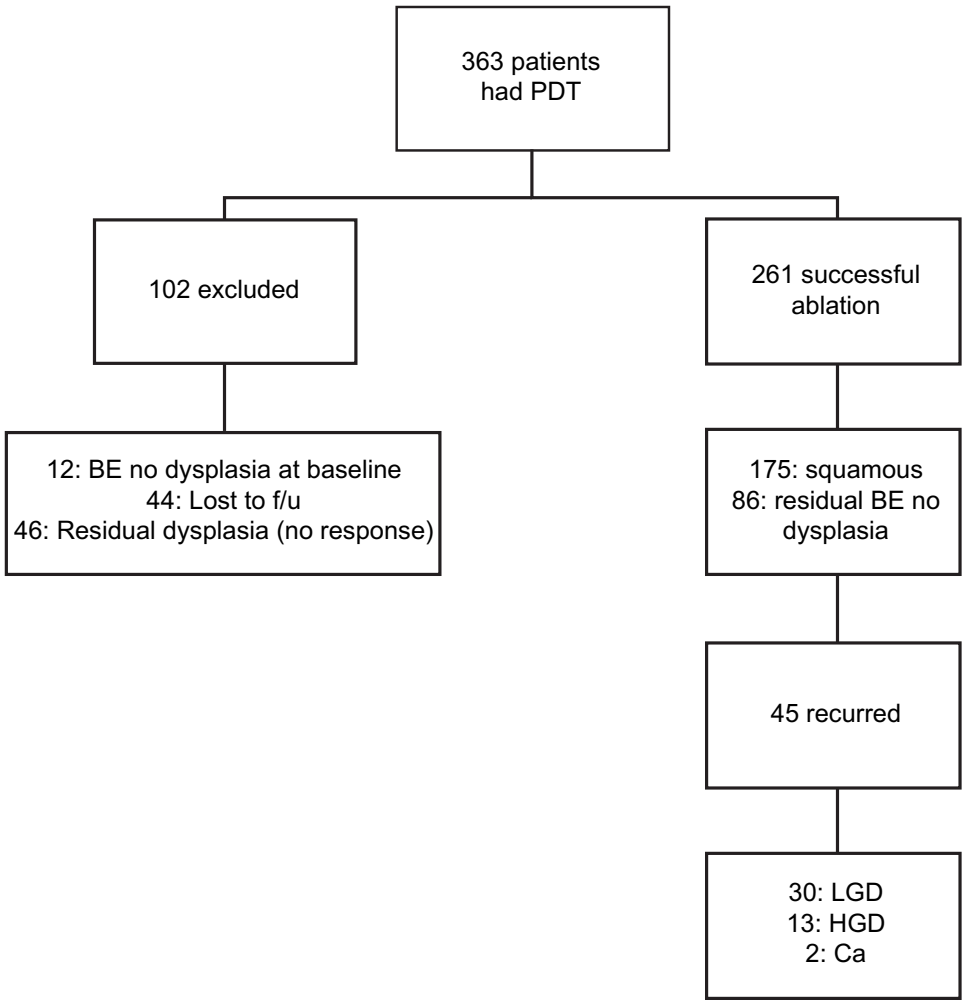


**Figure 1.** Description of patients included in the study. PDT, photodynamic therapy; BE, Barrett's esophagus; f/u, follow-up; LGD, low-grade dysplasia; HGD, high-grade dysplasia; Ca, carcinoma.

Statistical analysis was performed by using the JMP statistical analysis package (JMP, version 6; SAS Institute Inc, Cary, NC) and the S-plus statistical analysis package (Splus 8 Insightful Inc, Seattle, Wash). The Student *t* test was used to compare means and the Wilcoxon rank-sum test was used to compare medians as appropriate. The different factors abstracted were tested for possible univariate association with recurrence by using Cox proportional hazard regression. A time-to-recurrence analysis was performed, and a multivariate model was constructed to establish independent associations with the endpoint among the significant or clinically relevant predictors from the univariate model. Hazard ratios (HRs) from both univariate and multivariate analyses were calculated. We defined statistical significance as a $P$ value $< .05$.

## RESULTS

Figure 1 summarizes the study flow. A total of 363 patients underwent PDT between 1992 and 2005 with the following indications: BE with no dysplasia, 12 patients (3%); LGD, 56 patients (15%); HGD, 190 patients (52%); and intramucosal carcinoma, 105 patients (29%). Fifty-eight patients did not meet inclusion criteria: 12 patients with BE and no dysplasia at baseline and 46 patients who failed to achieve a response to PDT. Forty-four patients were lost to follow-up and were also excluded. A total of 261 patients were followed for a median follow-up time of 36 months (interquartile range 18-79 months). Of those patients, 220 were men (84%). Mean age was 65 ± 0.7 years (mean ± standard error of mean, range 30-92). All patients reported taking double-dose proton pump inhibitors as prescribed. Table 1 summarizes baseline characteristics of the patients.

A total of 261 patients were successfully ablated with an ablation outcome of squamous epithelium in 175 (67%) patients and BE with no dysplasia in 86 (33%) patients. Overall, 45 (17%) patients had recurrence of dysplasia/neoplasia during the follow-up period as follows: 30 patients with LGD, 13 with HGD, and 2 with intramucosal adenocarcinoma. Median time to recurrence was 17

**TABLE 1. Baseline characteristics of patients**

| Characteristic | Total no. patients (N = 261) | Patients with recurrence (n = 45) | Patients without recurrence (n = 216) | *P* value |
|---|---|---|---|---|
| Male | 220 (84) | 38 (84) | 182 (84) | 1.00 |
| Mean age (y) at entry ± SEM | | 67 ± 1.0 | 65 ± 0.8 | .85 |
| Hx of smoking | 191 (73) | 35 (78) | 156 (72) | .57 |
| Hx of ASA/NSAID use | 96 (37) | 16 (36) | 80 (37) | .98 |
| BMI >25 | 195 (75) | 30 (67) | 165 (76) | .18 |
| DH at endoscopy | 216 (83) | 41 (91) | 175 (81) | .12 |
| DH >2 cm | 178 (82) | 35 (78) | 143 (66) | .15 |
| BE >3 cm | 46 (18) | 18 (40) | 28 (13) | .0001 |
| EMR performed | 147 (56) | 24 (53) | 123 (57) | .74 |
| Stricture post-ablation | 59 (23) | 7 (16) | 52 (24) | .24 |

*SEM*, Standard error of the mean; *Hx*, history; *ASA*, aspirin; *NSAID*, nonsteroidal anti-inflammatory drug; *BMI*, body mass index; *DH*, diaphragmatic hernia; *BE*, Barrett's esophagus.
Except as otherwise indicated, figures given are number (%).

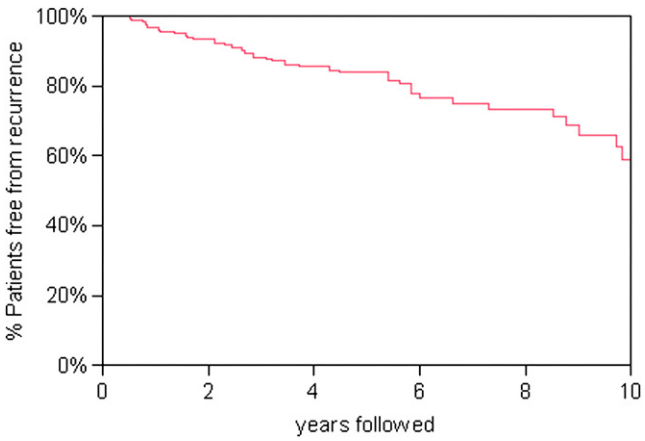


**Figure 2.** Kaplan-Meier curve estimating recurrence of dysplasia/neoplasia after successful ablation with PDT for all patients (N = 261).

months (interquartile range 8-45 months). Figure 2 shows the Kaplan-Meier curve of time to recurrence.

The preablation pathology of those 45 patients who had a recurrence was as follows: 14 LGD, 24 HGD, and 7 adenocarcinoma.

Categorical and continuous risk factors of recurrence of dysplasia/neoplasia are shown in Tables 2 and 3. On univariate analysis, performance of EMR, a BE segment longer than 3 cm, history of smoking (ever), BMI greater than 25, and an ablation outcome of BE were significant predictors of recurrence. Only age, history of smoking (ever smoked), and an ablation outcome of BE were significant predictors in the multivariate model. Table 4 summarizes the endoscopic appearance of recurrent dysplasia/neoplasia.

## DISCUSSION

In this article, we present data on recurrence rates and predictors of recurrence of dysplasia/neoplasia after PDT in a large cohort of patients with BE and dysplasia/neoplasia. Our data suggest that recurrence of dysplasia/neoplasia after PDT (cumulative recurrence rate of 17% after a median follow-up of 36 months) is associated with increasing age, presence of residual nondysplastic BE, and a history of current or recent smoking (within 30 days of ablation). Our definition of recurrence of dysplasia required patients to have negative findings on 2 upper endoscopies for any dysplasia 3 months apart after ablation to exclude the possibility of prevalent dysplasia. From our data, it seems that residual BE of any length makes recurrence of dysplasia more likely. In our practice, we perform ablation with the hope of achieving complete eradication of the BE.

Our study did not look at genetic biomarkers as predictors of recurrent dysplasia. We and others have previously reported persistence of genetic abnormalities in BE after PDT,[16] and this may very well be one of the most important mechanisms behind recurrence of dysplasia or resistance to PDT. This could be explained by the instability of the residual BE epithelium and its tendency to progress to dysplasia/neoplasia given persistent genetic abnormalities.

Smoking was a significant risk factor for recurrence of dysplasia in our study. It is known that tobacco smoking is a strong risk factor for squamous cell carcinoma of the esophagus, but its association with adenocarcinoma is controversial. Some studies showed that cigarette smoking is associated with worse GERD symptoms,[17,18]

**TABLE 2. Univariate analysis of factors predicting recurrence of dysplasia/neoplasia after photodynamic therapy**

| Risk factor | No. | Hazard ratio (95% CI) | *P* value |
|---|---|---|---|
| Female | 41 | 1.02 (0.45-2.29) | .962 |
| Age | | 1.02 (0.99-1.05) | .152 |
| Entry histology | | | |
| LGD | 53 | 0.75 (0.36-1.55) | .435 |
| HGD | 152 | 1.26 (0.69-2.30) | .459 |
| Cancer | 56 | 1.36 (0.59-3.13) | .465 |
| EMR performed | 147 | 2.05 (1.13-3.70) | .018 |
| BE ≥3 cm | 46 | 2.00 (1.09-3.66) | .025 |
| DH present | 216 | 0.96 (0.78-1.17) | .686 |
| DH length >2 cm | 178 | 1.08 (0.45-2.58) | .865 |
| >1 PDT/session | 58 | 1.00 (0.53-1.81) | 1.000 |
| Stricture | 59 | 0.78 (0.35-1.77) | .555 |
| Smoking ever | 191 | 2.81 (1.28-6.16) | .010 |
| ASA/NSAID use | 95 | 0.72 (0.38-1.35) | .302 |
| BMI <25 | 66 | 0.91 (0.84-0.99) | .021 |
| Ablation outcome | | | |
| Residual BE | 86 | 4.43 (2.04-9.58) | <.001 |
| Squamous epithelium | 175 | 0.80 (0.42-1.53) | .500 |

*CI*, Confidence interval; *LGD*, low-grade dysplasia; *HGD*, high-grade dysplasia; *BE*, Barrett's esophagus; *DH*, diaphragmatic hernia; *PDT*, photodynamic therapy; *ASA*, aspirin; *NSAID*, nonsteroidal anti-inflammatory drug; *BMI*, body mass index.

**TABLE 3. Multivariate analysis of factors predicting recurrence of dysplasia/neoplasia after photodynamic therapy (N = 261)**

| Risk factor | Hazard ratio (95% CI) | *P* value |
|---|---|---|
| Age | 1.04 (1.00-1.08) | .029 |
| BMI <25 | 0.93 (0.85-1.01) | .087 |
| Smoking ever | 2.68 (1.01-7.13) | .048 |
| Ablation outcome: residual BE | 2.88 (1.26-6.61) | .012 |

*CI*, Confidence interval; *BMI*, body mass index; *BE*, Barrett's esophagus.

**TABLE 4. Endoscopic appearance of recurrent dysplasia**

| Endoscopic appearance | No. patients |
|---|---|
| Irregular Z line | 17 |
| Islands of BE | 5 |
| Tongues of BE | 5 |
| Short-segment circumferential BE (<3 cm) | 5 |
| Long-segment circumferential BE (>3 cm) | 10 |
| Nodule | 3 |
| Buried or hidden dysplasia underneath squamous epithelium detected on biopsy | 0 |

*BE*, Barrett's esophagus.

whereas other studies failed to show an association.[19-21] Recently, Anderson et al[22] studied risk factors for adenocarcinoma and found that previous smoking or current smoking is a significant risk factor for the development of adenocarcinoma of the esophagus (odds ratio 1.72 and 4.84, respectively). Smoking has been shown to be associated with DNA damage in Barrett's mucosa, a mechanism that might explain the higher rate of recurrence in patients who ever smoked.[23]

Of 261 patients in our study, 45 had recurrence of dysplasia/neoplasia over a median follow-up of 36 months, leading to a cumulative recurrence rate of 17%. Most of our patients had recurrences in BE segments (28 patients), with the rest having recurrences around an irregular Z line (17 patients). Recurrence in 2 patients was as adenocarcinoma. These 2 patients had HGD in a long segment of BE (10 cm and 7 cm) before ablation. It is worth noting that none of our patients who had a recurrence had buried BE. This is in contrast to some studies that reported a rate as high as 5% of buried or hidden BE after porfimer-based PDT.[24-26] We do not believe that this is caused by a sampling error because we performed thorough biopsies every centimeter of the neosquamous segment. We believe that buried BE is rare after complete ablation of dysplasia has been performed. Recent data showed no difference in squamous overgrowth between patients who had PDT ablation and those who did not.[27] The clinical significance of buried BE is also controversial because some recent studies described decreased crypt proliferation and normal DNA content in buried BE, implying a low risk of progression to carcinoma,[28] whereas other studies described the development of adenocarcinoma from buried BE.[24,29-31]

Studies have shown that the rate of recurrence of dysplasia or neoplasia after endoscopic therapy of BE ranges from 3% to 30%.[14,32] Recently, Pech et al[12] identified several risk factors associated with recurrence. In this study with approximately 5 years of follow-up, these risk factors were piecemeal resection, a long-segment BE, lack of ablative therapy of residual BE, multifocal neoplasia, and more than 10 months until complete response. Most of these patients, however, did not undergo PDT, which makes it different from our study population. It has been suggested

in some studies that tight acid control might prevent recurrence of BE and dysplasia.[33] Although we did not specifically look at acid exposure after ablation, surrogates of acid reflux (presence and length of DH) were not significant predictors of dysplasia recurrence. Our data show that performing EMR is a risk for recurrence on univariate analysis, but this lost its significance when multivariate analysis was performed. Similar to the study by Pech et al,[12] EMR could be a surrogate for multifocal or residual disease or incomplete resection.

PDT is an ablative technique that has been widely used with good short- and long-term results.[8,11] Recently, Overholt et al[11] reported a multicenter 5-year efficacy and safety study of PDT for BE with HGD, but did not report the recurrence rate over a 5-year period. In addition, patients whose dysplasia recurred after ablation were still considered responders if dysplasia was not high grade. The rate of successful ablation in our study in an intent-to-treat analysis was 72% (261/363), considering the worst outcome of all those lost to follow-up as ablation failures. This is in line with other studies reporting an ablation rate of 60% to 80% with PDT.[30,34,35]

Identifying potential risk factors could help the gastroenterologist stratify patients who might benefit from a more rigorous surveillance program after ablation. Our results seem to suggest that closer follow-up might be warranted for those patients who are older, have a history of smoking, and have persistent BE after ablation. Based on our results, the goal of ablative therapy should be ablation of the entire BE segment given that residual BE was a predictor of recurrence. This, however, does not eliminate the need to continue surveillance in those patients in whom ablation of squamous epithelium was successful because 17 (38%) of 45 patients who had a recurrence had only an irregular Z line and no evidence of BE endoscopically.

There are some limitations to our study. It is known that dysplasia could be patchy and could be missed despite a thorough surveillance program. This means that some of the recurrences could have been prevalent dysplasia missed at the time of surveillance. Although this could be the case, we chose a strict definition of recurrence with negative findings on 2 endoscopies performed 3 months apart after ablation to decrease the risk of prevalent dysplasia. Another limitation in the study is the possibility of underestimating recurrences given the sampling difficulty in patients who had strictures after PDT. In our data, 59 (23%) patients had strictures as a complication of PDT. Based on previous work done by our group, the median time for stricture formation is 4 weeks,[15] and we typically proceed with dilation at that time if a stricture is found. Given that patients were included after findings negative for dysplasia in 2 endoscopies, this gave us enough time to proceed with dilation, and thus we do not believe that stricture formation affected our results.

To our knowledge, this study, which looked at the clinical predictors of recurrent dysplasia/neoplasia after successful ablation of BE with PDT, contained the largest cohort of patients. Although the use of PDT may decrease with the advent of newer effective ablation techniques such as radiofrequency ablation (RFA), it is a technique with long-term follow-up data that provide valuable information regarding the recurrence of dysplasia after successful ablation. This information is particularly important as attention shifts to surveillance after successful RFA, particularly in view of recent discussion on ablation being cost-effective in the management of patients with LGD or no dysplasia only if surveillance can be discontinued. Although RFA seems to be effective, these data underscore the importance of carefully following patients after RFA so that vital data on recurrence can be gathered and analyzed.

In conclusion, our results suggest that older age, a history of smoking, and residual BE after ablation predict recurrence of dysplasia and neoplasia after PDT. Smoking cessation and achieving complete eradication of any visible BE may decrease rates of recurrence.

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