Barrett's Esophagus after Bimodality Therapy in Patients with Esophageal Adenocarcinoma

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Keywords

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Abstract

Introduction: Barrett's esophagus (BE) may be present in patients with esophageal adenocarcinoma (EAC) after bimodality therapy (BMT). There is no specific guidance for follow-up of these patients with regard to the presence of BE or dysplasia. In this study, we assessed the outcomes of patients who, after BMT, had BE and those who did not. **Method:** Patients with EAC who had BMT were identified and analyzed retrospectively in two groups, with and without BE. We compared patient characteristics and outcome variables (local, distant, and no recurrence). **Results:** Of 228 patients with EAC, 68 (29.8%) had BE before BMT. Ninety-eight (42.9%) had BE after BMT, and endoscopic intervention was done in 11 (11.2%). With a median follow-up of 37 months, the presence

of post-BMT BE was not significantly associated with overall survival (OS) and local recurrence-free survival (LRFS). Similarly, endoscopic intervention was not significantly associated with OS and LRFS. Fifty (73.5%) patients with BE before BMT had BE after BMT ($p < 0.0001$). **Conclusion:** The presence of BE after BMT was not associated with increased risk of local recurrence. The local recurrence rate was not influenced by endoscopic intervention. Prospective studies are warranted to generate guidance for intervention, if necessary, for this group of EAC patients.

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Introduction

Esophageal adenocarcinoma (EAC) is the 6th common cause of cancer death worldwide [1]. In 2017, it was estimated that there would be 16,940 new cases and an estimated 15,960 people would die of this disease in the

US. The overall 5-year survival rate is 18.8%, but it is 42.9% for localized EAC and 23.4% for regional EAC [2]. Obesity, GERD, and the presence of Barrett's esophagus (BE) are the major risk factors for developing EAC. Patients with BE have 30–125 times greater risk of developing EAC than the general population [3, 4]. The annual risk of BE progression to EAC is reported to be between 0.5 and 1% [5–9].

Per current American College of Gastroenterology (ACG) guideline, suspected BE in normal population needs an endoscopy to document BE, and four-quadrant biopsies are recommended every 1–2 years. For patients with low-grade dysplasia and high-grade dysplasia without severe comorbidities, endoscopic therapy is recommended. Endoscopic resection (ER) is recommended for T1a lesions and diagnostic/therapeutic ER for T1b lesions. Following ER, ablation of the remaining high-risk tissue is also recommended. However, for the primary that is $\geq$ T2, patients are best treated with multimodality therapy [10]. Similarly, in the NCCN guideline 2017, it is recommended that after ER and ablation, patients need to be surveyed periodically based on the severity of the lesion at baseline [11]. However, no specific recommendations exist for how to tackle the persistence of BE with or without dysplasia in patients who have bimodality therapy (BMT). The recommendations have been left out mainly due to the lack of data. For patients who get surgery for EAC where high-risk esophagus is often removed, endoscopic surveillance is not recommended [11–14].

Patients who receive BMT are of special interest because they tend to develop more local events than those after trimodality [12, 15, 16]. We wanted to review the outcome of patients after BMT and focused mainly on the presence of BE/dysplasia versus no BE/dysplasia and patient outcomes. Such analysis has not been published, to our knowledge.

Methods

Patients

We identified patients from our prospectively maintained database in the department of GI Medical Oncology at the University of Texas MD Anderson Cancer Center between 2002 and 2015. We selected patients with EAC (esophagus, adenocarcinoma of esophagogastric junction [AEG] type I or II) [17] who received BMT. We selected patients who had at least two or more biopsies at different time points during the follow-up period. EAC staging was based on the American Joint Committee on Cancer staging manual (7th edition). We extracted demographics and clinical data, clinical staging, endoscopy and pathology reports, recurrence

and survival data. The institutional review board approved this analysis. Patient characteristics were compared in the two groups of patients with and without BE.

Treatment and Follow-Up

All patients had a radiation dose range of 40–66.3 Gy (intensity-modulated radiation therapy or proton). Eighty-one patients (35.5%) received induction chemotherapy prior to chemoradiation. Chemotherapy included a fluoropyrimidine with either a platinum compound, taxanes or rarely irinotecan. Twenty-three patients (10%) started with stage IV disease but were dispositioned to receive local consolidation chemoradiation after a favorable response to systemic chemotherapy; these decisions were made in the Esophageal Multidisciplinary Conference. Local and distant recurrences were defined by the imaging studies or endoscopy. Outcomes were categorized into 3 groups: (1) local recurrence, (2) distant recurrence, and (3) none. Follow-up time was calculated from the starting date of BMT to death or last visit.

Statistical Analysis

Patient characteristics are summarized using frequency (%) for categorical variables and median (range) for continuous variables. Wilcoxon rank sum tests or Kruskal-Wallis tests were performed to assess the differences in continuous variables between subgroups of patients. χ^2 tests or Fisher's exact tests were performed to assess the differences in categorical variables among subgroups of patients. Overall survival (OS) is defined as the time interval between diagnosis and the date of death due to any cause. Local recurrence-free survival (LRFS) is defined as the time interval between CTRT date and the date of local recurrence or death due to any cause. The probabilities of OS and LRFS were estimated using the method of Kaplan and Meier [18]. Cox proportional hazards regression models were fit to assess the association between OS or LRFS and patient characteristics [19]. The effectiveness of the endoscopic interventions as well as the outcomes were assessed including it in the Cox model as a time-dependent covariate. All statistical analyses were conducted in SAS and Splus.

Results

Characteristics of the Entire Population

Of the 228 patients, 208 (91.2%) were men. Of all patients, 185 (81.1%) were diagnosed with stage II–III. Sixty-eight patients (29.8%) had BE before BMT, and 98 patients (42.9%) had BE after BMT. BE was first diagnosed within the median of 5 months (range: 2–51) after BMT. Endoscopic interventions were performed in 11 patients with BE/dysplasia (Fig. 1).

Characteristics of Patients Based on the Presence of BE after BMT

Patient characteristics are outlined in two groups of BE and without BE in Tables 1 and 2. There was no difference between two groups with regard to age, gender, primary tumor length, and TNM staging. Higher percentage of

Fig. 1. Total patients with and without Barrett's esophagus (BE) after bimodality therapy (BMT). Asterisk signifies that 1 case had both local and distant recurrence after 6.5 years. The possibility of new primary tumor cannot be excluded.

patients with BE was in AEG1 (59.2%) compared to those without BE who had AEG2 (55.4%, $p < 0.0001$) (Table 1).

In the comparison of patients with and without BE after BMT, higher rate of BE before BMT was present in the first group than the second one (51 vs. 13.9%, $p < 0.0001$). Higher rate of dysplasia (high grade [HG] and low grade [LG]) before BMT was present in patients with BE compared to patients without BE (44.9 vs. 10.7%, $p < 0.0001$). Also, higher rate of dysplasia after BMT was found in patients with BE (HG in 29.6% and LG in 30.6%, respectively), compared to the group without BE (HG in 0% and LG in 0.8% respectively, $p < 0.0001$) (Table 2).

Recurrence and Survival Based on the Presence of BE after BMT

Patients were followed up for a median duration of 37 months (range: 6–157) after BMT. In patients with BE ($n = 98$), local recurrence was detected in 15 (15.3%) and in patients without BE ($n = 130$), it was detected in 19 (14.6%). There was no significant difference in the overall recurrence type between patients with and without BE (Table 2).

Patients with BE were evaluated based on recurrence type. Variables including age, tumor location, histology subtype, history of chronic GERD, and presence of BE/

dysplasia before BMT were not associated with the recurrence type (Table 3). In the local recurrence group ($n = 15$) and no-recurrence group ($n = 44$), BE was detected at a median of 6 months after BMT, while in the distant recurrence group ($n = 39$), BE was detected within a median of 3 months ($p = 0.007$).

Endoscopic intervention was performed only in 11 patients (Table 4). Three cases developed recurrences including 1 case that presented with distant metastases 2 years after BMT and 2 cases that presented with both local and distant recurrences (1 case within less than 1 year and the other one 6.5 years after BMT) (Table 4).

At the time of data collection, 42.2% of total patients were alive. Median OS was 49 months, with 3-year and 5-year survival rates of 61.3 and 44.4%, respectively. There was no difference in OS between patients with and without BE. Among patients with BE, 53.3% of patients in the local recurrence group were alive compared to 15.4% in distant and 75% in no-recurrence groups ($p < 0.0001$). Median LRFS in patients with BE was 43.4 months (95% confidence interval [CI], 28.2–60.7 months), with 3-year and 5-year LRFS rate of 55% (95% CI, 46–66%) and 41% (95% CI, 32–53%), respectively.

In the fitted Cox proportional hazards model for OS and LRFS among all 228 patients, BE was not significant-

Table 1. Summary of variables before bimodality therapy (BMT) based on Barrett's status ($n = 228$)

Covariate	Barrett's status after BMT		<i>p</i> value
	yes ($n = 98$)	no ($n = 130$)	
Age at diagnosis, years	67 [31–103]	67 [28–85]	0.52
Tumor length at diagnosis, cm	5 [1–13]	5 [1–13]	0.81
Gender			
Male	93 (94.9)	115 (88.5)	0.09
Female	5 (5.1)	15 (11.5)	
Siewert class			
Esophagus	13 (13.3)	3 (2.3)	<0.0001
AEG1	58 (59.2)	55 (42.3)	
AEG2	26 (26.5)	72 (55.4)	
NA	1 (1)	0	
Tumor histology subtype			
SRC	16 (16.3)	19 (14.6)	0.72
M	1 (1)	2 (1.5)	
M&SRC	3 (3.1)	5 (3.8)	
NE	3 (3.1)	1 (0.8)	
NOS	75 (76.5)	103 (79.2)	
Chronic GERD history			
Yes	60 (61.2)	78 (60)	0.85
No	38 (38.8)	52 (40)	
Barrett's before BMT (biopsy)			
Yes	50 (51)	18 (13.9)	<0.0001
No	48 (49)	112 (86.2)	
Barrett's length before BMT (endoscopy appearance)			
Long segment ≥ 3 cm	38 (76)	14 (63.6)	<0.0001
Short segment <3 cm	12 (24)	8 (36.4)	
Highest dysplasia before BMT (biopsy)			
HG	34 (34.7)	12 (9.2)	<0.0001
LG	10 (10.2)	2 (1.5)	
None	54 (55.1)	116 (89.2)	
Baseline T-staging			
T1	3 (3)	3 (2.3)	0.27
T2	15 (15.3)	10 (7.7)	
T3	74 (75.5)	109 (83.8)	
T4	3 (3)	3 (2.3)	
TX	3 (3.1)	5 (3.8)	
Baseline N-staging			
N0	36 (36.7)	51 (39.2)	0.37
N1	54 (55.1)	62 (47.7)	
N2	3 (3.1)	10 (7.7)	
N3	1 (1)	2 (1.5)	
NX	4 (1.1)	5 (3.8)	
Baseline M-staging			
M0	88 (89.8)	110 (84.6)	0.12
M1	6 (6.1)	17 (13.1)	
MX	4 (4.1)	3 (2.3)	
Baseline staging			
I	9 (9.1)	5 (3.8)	0.07
II–III	80 (81.6)	105 (80.8)	
IV	6 (6.1)	17 (13.1)	
NA	3 (3.1)	3 (2.3)	

Data are presented as median [range] or n (%). GERD, gastroesophageal reflux disease; M, mucinous; NE, neuroendocrine; NOS, not otherwise specified; NA, not available; SRC, signet ring cell.

Table 2. Summary of categorical and continuous variables after bimodality therapy (BMT), based on Barrett's status ($n = 228$)

a Categorical variables

Covariate	Barrett's status after BMT		<i>p</i> value
	yes ($n = 98$)	no ($n = 130$)	
Induction chemotherapy			
Yes	31 (31.6)	50 (38.5)	0.29
No	67 (68.4)	80 (61.5)	
Highest dysplasia after BMT			
HG	29 (29.6)	0	<0.0001
LG	30 (30.6)	1 (0.8) ^a	
None	39 (39.8)	129 (99.2)	
Recurrence type			
Local	15 (15.3)	19 (14.6)	0.54
Distant	39 (39.8)	61 (46.9)	
None	44 (44.9)	50 (38.5)	
Salvage esophagectomy			
Yes	11 (39.3)	13 (31)	0.47
No	17 (60.7)	29 (69)	
Survival status			
Alive	47 (48)	49 (37.7)	0.12
Dead	51 (52)	81 (62.3)	

Data are presented as n (%). HG, high grade; LG, low grade. ^a The biopsy reports at least low-grade columnar epithelial dysplasia without reporting any evidence of intestinal metaplasia.

b Continuous variables

Covariate/Barrett's status after BMT (yes/no)	<i>n</i>	Median [range]	<i>p</i> value
Frequency of endoscopic biopsy after BMT			
Yes	98	4 [2–14]	0.01
No	130	3 [2–11]	
Interval between Barrett's detection after BMT and BMT start date, months			
Yes	98	5 [2–51]	–
No	0	–	
Interval between BMT start date and local recurrence, months			
Yes	15	14.23 [6.14–95.41]	0.58
No	19	14.29 [5.65–38.77]	
Interval between Barrett's detection and local recurrence, months			
Yes	15	5.52 [0–84.3]	–
No	0	–	
Duration of follow-up after BMT start date, months			
Yes	98	43 [9–157]	0.007
No	130	32 [6–146]	

ly associated with the risk for death ($p = 0.43$) or the risk for local recurrence or death ($p = 0.84$). In the fitted Cox proportional hazards model for OS and LRFS among patients with BE, the endoscopic intervention was not significantly associated with the risk for death ($p = 0.34$) or the risk for local recurrence or death ($p = 0.63$).

Discussion

In this study on patients with EAC who had BMT, the main findings include; (1) endoscopic intervention for BE was not associated with decreased risk for local recurrence or death, although we acknowledge that the num-

Table 3. Summary of variables before bimodality therapy (BMT) in patients with BE, based on the recurrence ($n = 98$)

Covariate	Recurrence			<i>p</i> value
	local ($n = 15$)	distant ($n = 39$)	none ($n = 44$)	
Age at diagnosis, years	67 [53–83]	65 [31–103]	68 [50–79]	0.26
Tumor length at diagnosis, cm	5 [1–11]	6 [1–13]	4 [2–10]	0.01
Gender				
Male	14 (93.3)	38 (97.4)	41 (93.1)	0.65
Female	1 (6.7)	1 (2.6)	3 (6.9)	
Siewert class				
Esophagus	3 (20)	5 (12.8)	5 (11.4)	0.38
AEG1	7 (46.7)	27 (69.2)	24 (54.5)	
AEG2	5 (33.3)	6 (15.4)	15 (34.1)	
NA	0	1 (2.6)	0	
Tumor histology subtype				
SRC	4 (26.7)	7 (18)	5 (11.4)	0.59
M	0	0	1 (2.3)	
M&SRC	0	1 (2.6)	2 (4.5)	
NE	1 (6.7)	2 (5.1)	0	
NOS	10 (66.7)	29 (74.3)	36 (81.8)	
Chronic GERD history				
Yes	8 (53.3)	24 (61.5)	28 (63.6)	0.78
No	7 (46.7)	15 (38.5)	16 (36.4)	
Barrett's before BMT (biopsy)				
Yes	5 (33.3)	20 (51.3)	25 (56.8)	0.29
None	10 (66.7)	19 (48.7)	19 (43.2)	
Barrett's length before BMT (endoscopy appearance)				
Long segment ≥ 3 cm	5 (100)	16 (72.7)	17 (73.9)	0.41
Short segment < 3 cm	0	6 (27.3)	6 (26.1)	
Highest dysplasia before BMT (biopsy)				
HG	3 (20)	13 (33.3)	18 (40.9)	0.55
LG	1 (6.7)	4 (10.3)	5 (11.4)	
No	11 (73.3)	22 (56.4)	21 (47.7)	
Baseline T-staging				
T1	0	1 (2.6)	2 (4.5)	0.03
T2	0	3 (7.7)	12 (27.3)	
T3	15 (100)	30 (76.9)	29 (65.9)	
T4	0	3 (7.7)	0	
TX	0	2 (5.1)	1 (2.3)	
Baseline N-staging				
N0	5 (33.3)	8 (20.5)	23 (52.3)	0.05
N1	10 (66.7)	27 (69.2)	17 (38.7)	
N2	0	1 (2.6)	2 (4.5)	
N3	0	1 (2.6)	0	
NX	0	2 (5.1)	2 (4.5)	
Baseline M-staging				
M0	15 (100)	31 (79.5)	42 (95.5)	0.03
M1	0	6 (15.4)	0	
MX	0	2 (5.1)	2 (4.5)	
Baseline staging				
I	0	1 (2.6)	8 (18.2)	0.005
II-III	15 (100)	30 (76.9)	35 (79.5)	
IV	0	6 (15.4)	0	
NA	0	2 (5.1)	1 (2.3)	

Data are presented as median [range] or n (%). GERD, gastroesophageal reflux disease; M, mucinous; NE, neuroendocrine; NOS, not otherwise specified; NA, not available; SRC, signet ring cell; LG, low grade; HG, high grade.

Table 4. Summary of variables after bimodality therapy (BMT) in patients with BE, based on the recurrence ($n = 98$)

Covariate	Recurrence			<i>p</i> value
	local ($n = 15$)	distant ($n = 39$)	none ($n = 44$)	
Induction chemotherapy				
Yes	5 (33.3)	17 (43.6)	9 (20.5)	0.08
No	10 (66.7)	22 (56.4)	35 (79.5)	
Frequency of endoscopic biopsy after BMT	4 [2–14]	2 [2–6]	5 [2–13]	<0.0001
Frequency of Barrett's after BMT (total)	2 [1–6]	2 [1–6]	3 [1–9]	
Interval between Barrett's detection after BMT and BMT start-date, months	6 [2–27]	3 [2–29]	6 [2–51]	0.006
Highest dysplasia after BMT				
HG	7 (46.7)	13 (33.3)	9 (20.4)	0.37
LG	3 (20)	12 (30.8)	15 (34.1)	
None	5 (33.3)	14 (35.9)	20 (45.5)	
Frequency of HG dysplasia after BMT (biopsy)				
0	8 (53.3)	26 (66.7)	35 (79.5)	0.12
1	5 (33.3)	9 (23.1)	8 (18.2)	
2	1 (6.7)	4 (10.2)	1 (2.3)	
3	1 (6.7)	0	0	
Frequency of LG dysplasia after BMT (biopsy)				
0	5 (33.3)	15 (38.5)	20 (45.5)	0.30
1	3 (20)	10 (25.7)	9 (20.5)	
2	4 (26.7)	7 (17.9)	2 (4.5)	
3	3 (20)	7 (17.9)	13 (29.5)	
Local recurrence at same site of previous Barrett's				
Yes	8 (53.3)	9 (69.2)	NA	0.23
No	4 (26.7)	4 (30.8)		
Equivocal	3 (20)	0		
Local recurrence at same site previous dysplasia				
Yes	6 (40)	4 (30.8)	NA	0.14
No	6 (40)	9 (69.2)		
Equivocal	3 (20)	0		
Local recurrence with concurrent Barrett's				
Yes	10 (66.7)	6 (42.9)	0	0.20
No	5 (33.3)	8 (57.1)	0	
Endoscopic intervention				
Yes	0	3 (7.7)	8 (18.2)	0.10
No	15 (100)	36 (92.3)	36 (81.8)	
Endoscopic intervention frequency				
0	15 (100)	36 (92.3)	36 (81.9)	0.58
1	0	2 (5.1)	2 (4.5)	
2	0	1 (2.6)	3 (6.8)	
3	0	0	1 (2.3)	
8	0	0	2 (4.5)	
Follow-up duration after BMT, months	42 [13–157]	26 [9–84]	55 [19–151]	<0.0001
Survival status				
Alive	8 (53.3)	6 (15.4)	33 (75)	<0.0001
Dead	7 (46.7)	33 (84.6)	11 (25)	

Data are presented as median [range] or n (%). LG, low grade; HG, high grade.

ber of cases that received this intervention is too small; (2) with a median follow-up of 37 months since BMT, there was no significant difference in recurrence and survival rates; and (3) patients with BE had mostly AEG1 tumor, but patients without BE had mostly AEG2.

Several studies evaluated the role of endoscopic intervention in decreasing progression rate of BE/low-grade dysplasia to EAC [20–23]. However, the data on the beneficial effect of procedure for treatment of BE after BMT are very limited. In our patients with BE, only 11.2% underwent endoscopic procedures for BE/dysplasia, and the reason for no procedure in the remainders is unknown. Barthel et al. [24] analyzed retrospectively the efficacy and safety of cryoablation for persistent dysplastic BE in 14 patients who achieved complete clinical response after BMT. They reported a significant reduction in median circumferential and maximal Prague criteria accompanied by downgrading of dysplasia in all 14 patients with a median number of 1 sessions and a median follow-up time of 7 months from initial cryoablation.

In our study, BE after BMT was not significantly associated with OS and LRFS. While poorer prognosis was found for patients after trimodality, if they showed BE prior to trimodality [25, 26], no study has evaluated the prognostic role of BE after BMT.

In our study, most patients with BE had a history of BE before BMT, and they also had AEG1 compared to AEG2 in patients without BE. Tumor location is not assessed in reported studies in patients with BE after BMT. However, Cen et al. [26] showed higher rate of AEG1 in patients with history of BE before trimodality.

Among studies that investigated persistent BE after chemoradiation in patients with EAC [24, 27], Barthel et al. [24] identified persistent BE on surveillance endoscopy in 14 out of 16 patients after BMT. They reported that surveillance endoscopy every 6 months and beyond detected all cases with reappearance of BE visible both endoscopically and on histology. They argued that concurrent detection of BE reappearance with the resolution of therapy-related acute mucosal inflammation supports the persistence of pre-treatment tumor-associated BE, rather than reflux-related recurrence of BE [24]. They also suggested that surveillance for persistent BE should begin 6 months after BMT [27]. In our study, the median time for the detection of BE was 5 months from the BMT, and 48% of patients were detected to have BE at the first biopsy which was taken within 2.7 months after BMT (data not shown).

With regard to risk factors for BE progression, prior studies mostly evaluated clinical risk factors for progres-

sion of BE before BMT or TMT rather than risk factors for progression of BE after BMT. Although male patients are reported to have a higher chance of progression to EAC than female patients [5, 28–31], in patients with BE after BMT, gender was not a significant risk factor neither for the development of BE nor for the recurrence (Table 1, 3). With regard to the length of BE, while there are controversial reports on the incidence rate of progression of short-segment BE (0.07–0.61%) and long-segment BE (0.22–0.67%) to EAC [28, 30–35], its prognostic role in recurrence after BMT is not evaluated. In our study, we found significantly more patients with long-segment BE ≥ 3 cm in patients with BE but we did not find any significant difference in the length of BE among local, distant, and no recurrence groups (Table 3).

Dysplasia is one of the most established risk factors for the progression of BE to EAC [36]. In our study, patients with BE had a significantly higher rate of dysplasia before (HG: 34.7%, LG: 10.2%) and after BMT (HG: 29.6%, LG: 30.6%). However, recurrence type was not significantly associated with dysplasia before and after BMT (Table 3, 4). In the recent years, biomarker studies have been conducted to give a better prediction of progression of BE/dysplasia to EAC [37–39]; however, no study is available regarding biomarkers of BE progression to EAC recurrence after BMT.

There are certain limitations to this study. On one hand, we did not find the beneficial role of BE diagnosis and an intervention for it in decreasing recurrence rate during follow-up, but one should notice that progression of BE to EAC might occur even after 10 years or more [5] and EAC would be detected in a very long-term follow-up. One more challenging issue is whether the local recurrence is a new EAC or not; although a new EAC is expected to occur years later compared to relapse. It should also be noted that endoscopic biopsy after chemoradiation might not show an existing residual tumor due to sampling limitations. In a large study, 322 patients with esophageal cancer who underwent preoperative chemoradiation showed negative post-chemoradiation biopsy in 79% while only 21.7% had a pathCR on their surgical specimens [40]. The negative predictive value of the pathology report after chemoradiation is around 30% [41–43]. In addition, the number of our patients with BE before BMT is likely underestimated as BE lesions might not be biopsied during the endoscopy for the initial tumor staging.

All in all, the aim of this study was to look into the prognostic role of BE after BMT and if endoscopic intervention makes any difference. Due to the retrospective nature of this study and the mentioned challenging issues, we can-

not make a recommendation on the appropriateness of endoscopic intervention for BE/dysplasia after BMT. A panel of biomarkers might be helpful in forecasting recurrence. Further bench and prospective clinical studies might reveal more information in this area.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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