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ORIGINAL ARTICLE

A clinicoepidemiological study of esophageal cancer patients at the National Cancer Institute, Cairo University, Egypt

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Abstract

Objective The purposes of this study were to (1) assess the clinicoepidemiological characteristics of esophageal cancer patients, (2) analyze the prognostic factors determining treatment failure and survival, and (3) evaluate the results of various treatment modalities for locoregional and disseminated disease and their effect on disease-free survival and overall survival (OS).

Methods Clinicoepidemiological retrospective data from 81 esophageal cancer patients treated at the National Cancer Institute of Cairo between 2007 and 2011 were evaluated.

Results The study showed that patients with esophageal cancer commonly present with locally advanced disease (87.7% had T-stage 3 and 12.3% had T-stage 4). There was a significant correlation between surgery and survival; patients who received radical surgery and postoperative radiation had a better median survival than patients who received radical radiotherapy (20 months vs. 16 months, respectively; $P = 0.04$). There was also a significant statistical correlation between radical concomitant chemoradiotherapy (NCRT) and palliative treatment. Patients who received radical NCRT had a better median survival than patients who received palliative radiotherapy (16 months vs. 10 months, respectively; $P = 0.001$). The median follow-up period for all patients was 7 months. The median OS of the whole group was 12 months. The OS after 1 and 2 years was 57.8% and 15%, respectively.

Conclusion High-dose NCRT is an acceptable alternative for patients unfit for surgery or with inoperable disease. High-dose radiation is more effective than low-dose radiation in terms of local control, time to relapse, and OS. Further study using a larger series of patients and introducing new treatment protocols is necessary for a final evaluation.

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Key words: esophageal cancer; epidemiology; retrospective trial

Esophageal cancer is a malignancy with a high mortality rate. In the United States 16,980 people are diagnosed with esophageal cancer each year and 14,710 die of the disease. According to data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, the 5-year survival rate for patients with esophageal cancer has shown a modest improvement over the last 30 years, from 5% in the years 1975 to 1977 to 17% during the period 2001 to 2007. These dismal results are thought to reflect the propensity for early tumor dissemination and an advanced stage of disease at diagnosis [1].

Esophageal cancer represents 6–8% of all malignancies in Egypt. Affected patients have a mean age of 58.7 years and the male to female ratio is 1.9. Data from the Gharbeya population-based registry conducted in 2002 showed that approximately 40% of the tumors are found in the lower third of the esophagus, 40% at the gastroesophageal junction (GEJ), 13% in the middle esophagus, and 7% in the upper esophagus. Histologically, 53% of the tumors are squamous cell carcinomas (SCCs) and 18% are adenocarcinomas.

During the 1960s, in the United States, SCCs ac-

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counted for more than 90% of all esophageal cancers, and esophageal adenocarcinomas were considered so uncommon that some authorities questioned their existence. For the past 2 decades, however, the incidence of esophageal adenocarcinomas has increased dramatically in Western countries, such that both these tumors now occur with almost equal frequency [2].

Although significant advances have been made in the treatment of esophageal cancer, this aggressive malignancy commonly presents as locally advanced disease with a poor prognosis despite improvements in the detection of pre-malignant lesions on pathology [2].

Management of esophageal cancer is a challenging problem because most patients with potentially metastatic locally advanced disease present in a poor general condition. However, early and effective neo-adjuvant chemoradiotherapy (NCRT) and surgical resection could lead to increased survival [3].

The aims of this study were as follows:

1. Analyze the clinicoepidemiological characteristics of patients with esophageal cancer.

2. Evaluate the prognostic factors affecting failures (local and distant) and survival.

3. Assess the results of different treatment modalities for locoregional and disseminated disease and their effect on disease-free survival and overall survival (OS).

Materials and methods

This was a retrospective study of 81 patients with esophageal cancer who were treated at the National Cancer Institute of Cairo from 2007 to 2011. All patients with esophageal cancer, including those with metastatic disease, were eligible for inclusion.

Data obtained from the patients' files included: the patient's serial number; age; family history; smoking history; date of presentation; patient's complaint; clinical examination; biopsy date; surgery date; type of surgery; tumor site; tumor size, histological type and grade; lymph node status; tumor-node-metastasis (TNM), chemotherapy and radiotherapy data; time of occurrence; site of relapse (locoregional or distant); and date and condition of the patient during the last visit.

Statistical analysis

The data were summarized using descriptive statistics (mean, frequencies). Mean values and standard deviations were compared using a simple *t* test (2 variables). Percentages were compared using the Chi-square test or Fisher's exact test. Logistic regression was used whenever the dependent factor was binary in nature during multivariate analysis. The Kaplan-Meier test was used for predictive survival rates. Data were analyzed using SPSS software (Version 15; SPSS Institute, USA). A *P* value less than 0.05 was considered statistically significant.

Results

The mean age of the 81 patients included in this study was 60 years; 8 patients (9.9%) were less than 40 years old. The incidence of esophageal cancer increased in patients over 40 years of age and peaked between 50 and 70 years of age.

Fifty-three patients (65%) were men and 28 were women (35%), with a male to female ratio of 1.9:1.

The main presenting complaint was dysphagia occurring with the ingestion of solid food (reported by 45 patients; 53.6%) or solid food and liquids (36 patients; 44.4%). Twenty-six patients (32%) complained of nausea and vomiting. Loss of weight was found in 53 patients (65%).

Forty-four patients (54%) were heavy smokers and 37 patients (46%) were non-smokers.

At the time of presentation, the performance of the patients was recorded using the Eastern Cooperative Oncology Group scoring system. Thirty-three patients (40.7%) had a score of 1–2 and 48 patients (59.3%) had a score of 3–4.

Tumor staging using the American Joint Committee on Cancer TNM staging system revealed that all the patients had advanced disease (Type 3, 87.7% and Type 4, 12.3%). Positive nodal metastases were found in 61 patients (75.3%).

Only 34 patients (42%) had operable disease. Twenty patients underwent total esophagectomy and gastric pull-up and 1 patient underwent a partial esophagectomy. All patients received post-operative radiation. Thirteen patients (16%) were medically unfit for surgery and received radical NCRT using a 10 mV LA machine.

Forty-seven patients (58%) received palliative radiation, 13 patients (16%) received a high dose (50–55 Gy) for 5–6 weeks, and 34 patients (42%) received a low dose (30 Gy) for 2 weeks.

Patients who received radical NCRT underwent a complete chemotherapy (CCT) course; 12/13 patients received 4–6 CCT cycles, compared to 2/14 patients in the palliative radiotherapy (PRT) group. Twelve patients in the palliative group received 1–3 cycles.

Treatment outcome was evaluated based on treatment response, local failure, systemic failure, and OS.

Local response to treatment was assessed in 60 patients based on radiological and clinical information. Eleven patients (18.3%) had a partial response, 10 patients (38.8%) had static disease, and 8 patients (16.6%) had progressive disease. Unfortunately, no complete responses were recorded. The response to treatment could not be evaluated in 26 patients due to a lack of post-treatment radiological information.

Table 1 Parameters affecting local response

Characteristics	Number	Partial response	Stationary	Progressive	*P* -value
Total (*n*)	37	13	11	13	
Age (years)					
≤ 60	15	40.0%	33.4%	26.7%	0.671
> 60	22	31.8%	27.3%	40.9%	
Performance status					
1 & 2	15	53.3%	40.0%	6.7%	0.010
3 & 4	22	22.7%	22.7%	54.5%	
Pathology					
SCC	22	40.9%	31.8%	27.3%	
Adenocarcinoma	13	23.1%	30.8%	46.2%	0.543
Undifferentiated	2	50.0%	0	50.0%	
T-stage					
T3	26	30.8%	30.8%	38.5%	0.676
T4	11	45.5%	27.3%	27.3%	
Treatment					
Radical NCRT	7	4.9%	42.9%	14.3%	0.424
PRT	30	33.3%	26.7%	40.0%	
PRT					
High dose PRT	8	62.5%	25.0%	12.5%	0.044
Low dose PRT	22	18.2%	27.3%	54.4%	
PRT ± CCT (Cisplatin based chemotherapy)					
PRT + CCT	6	33.3%	33.3%	33.3%	0.399
PRT – CCT	16	12.5%	25.0%	62.5%	
NCRT (cisplatin based CCT) vs. high dose PRT (without CCT)					
NCRT	7	42.9%	42.9%	14.3%	0.727
High dose PRT	8	62.5%	25.0%	12.5%	
Number of chemotherapy cycles (cisplatin based chemotherapy)					
1–3 cycles	5	0	40.0%	60.0%	0.063

Analysis of the correlation between the local response to treatment (measured as the percentage of persistent or partial tumor regression after 6 months) and the prognostic parameters was performed using the log-rank test (Table 1).

Among patients with performance status 1 and 2, 53% had partial regression (PR) and 6.7% had progressive disease compared to 22% and 54.6%, respectively, among patients with performance status 3 and 4; the difference was statistically significant ($P = 0.01$).

High doses of radiation either alone or with NCRT (50–65 Gy/5-6 wks) achieved PR in 62% of patients compared to in 18% when using low-dose radiation (30 Gy/2 wks); the difference was statistically significant ($P = 0.044$).

Patients who received 4–6 cycles of CCT achieved a PR in 62% compared to no regression in patients who received 1–3 cycles ($P = 0.06$). There were no statistical differences among patients based on age, histological type, or T-stage.

After surgical excision, only 1 patient had a local recurrence 14 months after surgery; he received additional radiation and CCT.

Nine patients had systemic failure, 6 had bone metastases, 2 had lung metastases, and 1 had peritoneal nodules.

The OS was estimated using the Kaplan and Meier test, and different prognostic parameters were compared with the log-rank test. All significant variables were entered into the Cox Proportional Hazards Model (sex, smoking, site, T-stage, N-stage, and radiotherapy).

The median follow-up period for all patients was 7 months. The median OS was 12 months. The OS after 1 and 2 years was 57.8% and 15%, respectively (Fig. 1).

Analysis of the parameters affecting (OS showed that the OS was not affected by age, histological type, T-stage, or N-stage.

Performance status, tumor site, and treatment modality had a statistically significant impact on OS (Table 2).

The 1-year OS of patients with performance status 1 and 2 was 72.7% and the median survival was 18.2 months vs. 47.3% and 10.2 months for patients with performance status 3 and 4 ($P = 0.01$; Fig. 2).

Patients with tumors located in the middle third of the esophagus had a median survival of 16.4 months, which was better than the survival of patients with tumors in the upper or middle third of the esophagus. The 2-year OS of patients with GEJ tumors was 27%, and the median

Table 2 Parameters affecting OS

Factors	Cases	1-year survival (%)	2-year survival (%)	Median survival (months)	*P*-value
All patients	81	57.8	15.0	12.0	
Age (years)					
≤ 60	40	65.8	12.6	16.1	0.266
> 60	41	50.1	23.0	12.0	
Performance					
1 & 2	33	72.7	17.5	18.2	0.010
3 & 4	48	47.3	17.7	10.2	
Site					
Upper 1/3	13	20.5	0	8.0	
Middle 1/3	32	70.3	16.1	16.4	0.036
Lower 1/3	10	70.0	0	14.0	
GEJ	26	58.1	27.1	12.0	
T stage					
T3	71	92.3	21.1	13.1	0.541
T4	10	50.7	14.5	12.0	
N stage					
Positive lymph nodes	61	56.6	20.3	12.2	0.729
Negative lymph nodes	20	61.4	12.6	13.0	
Pathology					
SCC	55	54.7	12.1	15.0	
Adenocarcinoma	22	60.3	22.3	13.0	0.258
Undifferentiated carcinoma	4	0	0	7.0	
Treatment					
Radical NCRT	13	74.6	22.4	16.1	
PRT	47	27.2	0	10.0	< 0.001
Surgery + posterative radiotherapy	21	85.7	31.1	20.1	
Radical NCRT vs. surgery + posterative radiotherapy					
Radical NCRT	13	74.6	22.4	16.1	0.040
Surgery + posterative radiotherapy	21	85.7	31.1	20.1	
PRT					
High dose PRT	13	38.4	0	10.1	0.037
Low dose PRT	34	7.9	0	7.0	
Low dose PRT ± CCT (Cisplatin based chemotherapy)					
PRT + CCT	14	13.4	0	10.2	0.007
PRT – CCT	20	0	0	5.2	
NCRT vs. high dose PRT (without chemotherapy)					
NCRT (cisplatin based chemotherapy)	13	74.6	22.4	16.1	0.047
High dose PRT	13	38.4	0	10.1	
Number of chemotherapy cycles					
1–3 cycles (cisplatin based chemotherapy)	13	0	0	8.5	0.001
4–6 cycles (cisplatin based chemotherapy)	14	76.0	20.3	16.1	

survival time was 12 months. Patients with tumors in the middle third of the esophagus had a 16% survival and a median survival time of 16 months. Patients with tumors in the upper or lower third of the esophagus had a 0% survival ($P = 0.036$; Fig. 3).

Patients who underwent surgical treatment followed by posterative radiotherapy had the best OS (85.7%) after 1 year ($P < 0.001$; Fig. 4).

Patients who underwent surgical treatment followed by posterative radiotherapy had better OS (85.7%) after 1 year, than those patients who received NCRT without surgical intervention (74.6%; $P = 0.04$; Fig. 5).

Survival rate was higher (median survival, 10.1 months) among patients who received high-dose PRT (45–50 Gy). For patients who received low-dose PRT (30 Gy), the median survival was 7 months ($P = 0.037$; Fig. 6).

Patients who received high-dose PRT without CCT had an OS of 38.4% at 1 year. Patients who received radical NCRT (cisplatin-based CCT) had an OS of 74.6% at 1 year (P = 0.047; Fig. 7), a significant difference.

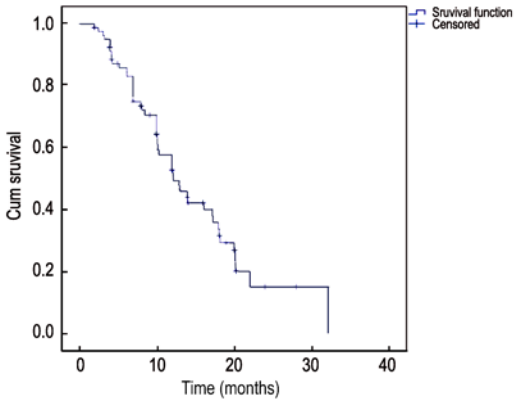

Fig. 1 OS curve of the patient group

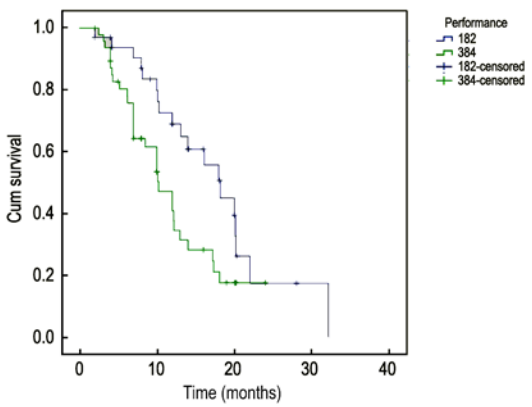

Fig. 2 OS based on performance status

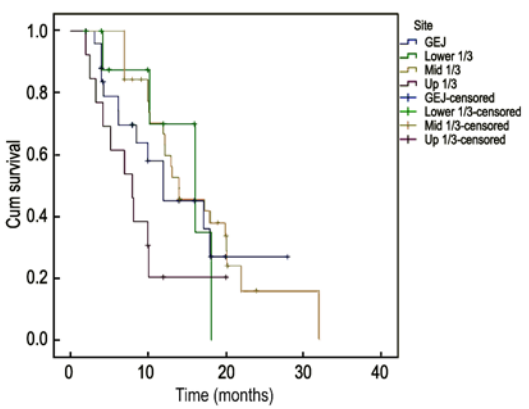

Fig. 3 OS based on tumor site

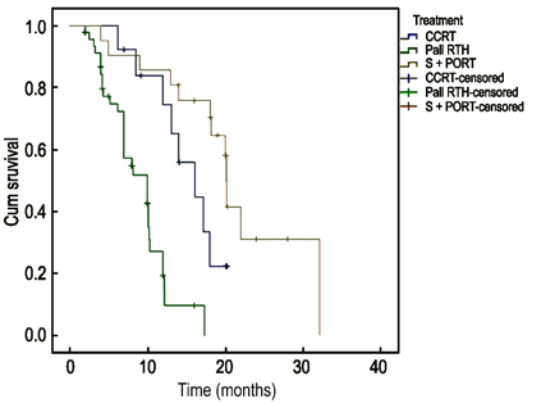

Fig. 4 OS based on type of treatment

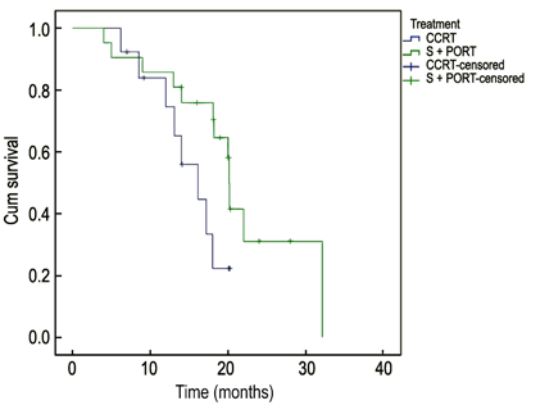

Fig. 5 OS based on surgery vs. radical concomitant chemoradiotherapy

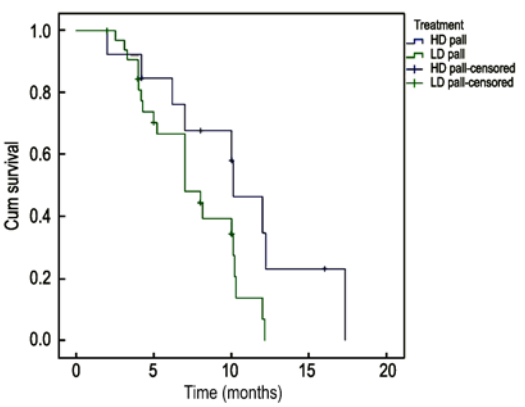

Fig. 6 OS based on palliative radiotherapy dose

There was also a significant difference in survival time based on PRT with and without CCT. Patients who received PRT concomitant with CCT (cisplatin-based CCT) had a median survival of 10.2 months; those who received PRT only without CCT had a median survival of 5.2 months ($P = 0.007$; Fig. 8).

Patients who received 4–6 CCT cycles had an OS of 76% at 1 year compared to patients who received only 1–3 CCT cycles and had an OS of 0% at 1 year ($P = 0.001$; Fig. 9).

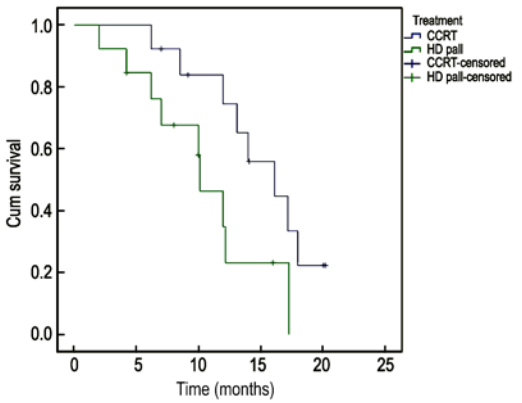

Fig. 7 OS based on the palliative radiotherapy dose vs. radical concomitant chemoradiotherapy

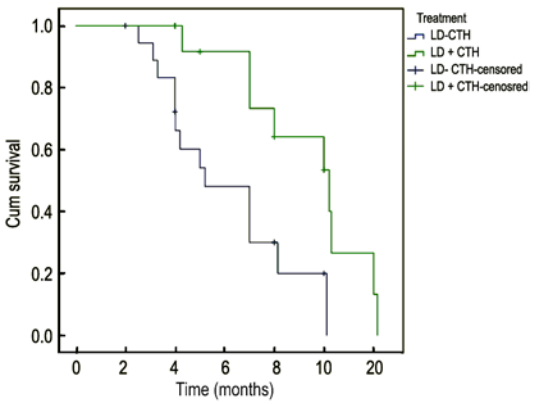

Fig. 8 OS based on the palliative radiotherapy dose with and without chemotherapy

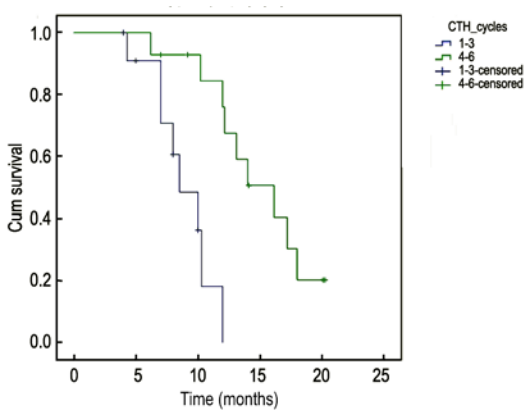

Fig. 9 OS based on the number of chemotherapy cycles

Discussion

This study profiled esophageal disease among Egyptian patients and analyzed the results of different treatment modalities and their effect on locoregional control, distant metastases, and OS.

Our findings were comparable to data reported in the literature regarding the predominance in men and tumor site predilection; however, we observed a younger age incidence (49% of our patients were below 60 years of age) and a late presentation among our patients.

In our study, the clinical stage, histological type, treatment modality, and radiation dose were significant parameters that affected OS and local control. Smoking was considered an etiological risk factor for esophageal cancer; 54% of the patients were heavy smokers (more than 20 cigarettes/day). This also was reported by Freedman et al., who considered tobacco and alcohol abuse as major risk factors for SCC, whereas the use of tobacco is a moderate established risk factor for adenocarcinoma [4]. Cook *et al.* reported that the risk of esophageal SCC decreased substantially after smoking cessation [5].

In our study, the OS at 1 year of patients who had SCC was 54.7% compared to 60.3% among adenocarcinoma patients. Similar results were reported by Rice [6].

We found a significantly better survival with surgical treatment followed by post-operative NCRT compared to surgery alone. The OS at 1 and 2 years among patients who underwent surgery followed by posterative radiotherapy was 88.9% and 31%, respectively. However, only 30% to 40% of patients had potentially resectable disease at the time of presentation. Among patients who did not undergo surgery and who were treated using other modalities such as radical NCRT and PRT, the 1-year survival was 61.9% and 36.1%, respectively, a significant difference ($P < 0.001$). These results were comparable to those of Walsh et al. who observed that while surgery had been the standard treatment for early esophageal cancer, only 5% to 20% of those undergoing surgery alone lived for 3 to 5 years [7].

Adelstein *et al* evaluated post-operative NCRT in tumors with positive nodes and found that the 4-year OS and locoregional control were 86% and 56%, respectively, which were better than surgery alone [8].

Kofoed *et al* reported that post-operative NCRT has been associated with a survival benefit in lymph node-positive patients; the 3-year OS after post-operative NCRT was 37% compared to 24% after surgery alone [9].

The better results reported by Adelstein *et al.* and Kofoed et al. might be explained by the prevalence of early stage and lower third esophageal tumors among their patients.

In our study, the OS of radical NCRT and high-dose PRT (45–60 Gy) alone were compared, and we found that, despite the poor OS rates with both treatment modalities, patients who received NCRT had a better OS than those who received radiation alone (61.9% vs. 51.2%, respectively; $P = 0.002$).

Conroy *et al* also reported the efficacy of radical treatment in patients with locally advanced esophageal cancer. At a median follow-up of 18 months, the median OS time was 23 months [10].

Comparable results were also reported by Cooper *et al*. who compared PRT alone vs. NCRT in patients with locoregional thoracic esophageal cancer. He reported a significant survival advantage for NCRT (5-year OS 27% vs. 0%). Owing to the results of this trial, definitive NCRT was considered the standard of care for patients with inoperable disease [11].

Conclusions and recommendations

As esophageal cancer is a very aggressive tumor, most patients present with advanced late-stage disease that is beyond radical treatment. Health education and screening programs are advisable for earlier tumor detection because the tumor stage is the most important prognostic factor for better survival rates.

High-dose NCRT is an acceptable alternative for patients unfit for surgery or with inoperable disease.

High-dose radiation is more effective than low-dose radiation regarding local control, time to relapse, and OS.

Further studies in a larger patient series and including new treatment protocols is necessary for a final evaluation. Patients should become more involved in clinical trials to achieve the best treatment strategy for this aggressive disease.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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