Prognostic risk factors for T1 thoracic esophageal cancer: a retrospective cohort study

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Background: Esophageal cancer has a poor overall prognosis and a high incidence of post-treatment complications. This study aimed to analyze the common surgical methods for treating T1 thoracic esophageal cancer and explore its prognostic risk factors to provide a basis for appropriate treatment selection.

Methods: In this population-based retrospective cohort study, data of patients diagnosed with T1 thoracic esophageal cancer from 2010 to 2016 were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. Patients were divided according to those who had surgery and those who had radiotherapy. Survival curves were generated using the Kaplan-Meier method and validated by the log-rank test. Cox's regression model was used to analyze the independent prognostic risk factors.

Results: Overall, 2,027 eligible patients, including 824 and 1,203 patients in the surgical and non-surgical groups, respectively, were analyzed. There was no significant difference in survival between the surgical and non-surgical groups (P=0.79). In subgroup analysis, the Cox regression analysis showed that radiotherapy was a significant prognostic factor (P=0.00059).

Conclusions: The impact of surgery on patients with T1 thoracic esophageal cancer was insignificant; however, radiotherapy was an independent prognostic risk factor. These results provide a reliable basis for clinical treatment of patients with T1 thoracic esophageal cancer.

Keywords: Esophageal cancer; Surveillance, Epidemiology, and End Results database (SEER database); prognostic risk factors; surgery; radiotherapy

Introduction

Esophageal cancer is a malignant tumor with a poor prognosis. According to the American Cancer Society, the incidence of esophageal cancer and its mortality rate in 2020, were ranked seventh and sixth among malignant tumors, respectively; it results in approximately 450,000 deaths annually (1,2). In the Netherlands and several other western countries, Chemoradiotherapy followed by surgical resection is the preferred treatment for esophageal cancer (3). With the progress of genomics and molecular research, as well as the emergence of immunotherapy and targeted therapy, our understanding of esophageal cancer has been improved, so that we can find more new methods (4-7). At the same time, with the progress of surgery (standardization of resection scope and lymph node resection, progress of perioperative care, progress of minimally invasive and robot assisted technology), opportunities are provided to improve tumor and surgical results (8-10). Due to its low invasiveness, chemoradiotherapy
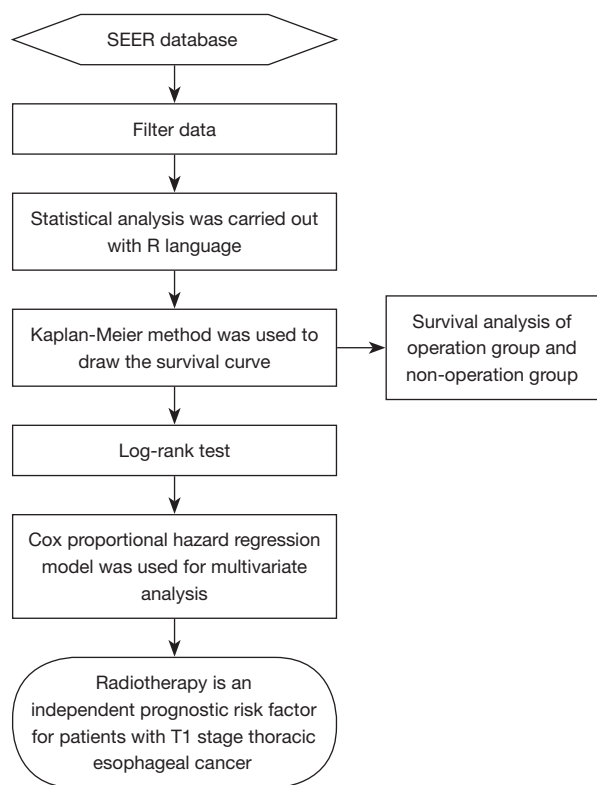
Figure 1 Flow diagram.

has become the standard treatment for patients with locally unresectable esophageal squamous cell carcinoma (ESCC) (11). For patients who are unable or unwilling to undergo surgery, chemoradiotherapy is recommended (12).

In the past two decades, the treatment of esophageal cancer has developed from simple surgery to multimodal treatment (surgery combined with chemotherapy or radiotherapy and chemotherapy) (13). This change has brought great benefits to patients. Five-year survival rates for esophageal cancer have doubled in some high-income countries, according to the International Cancer Benchmark Partnership report (14,15). Data from the National Cancer Database (USA) showed that the survival rate of multimodality therapy was double that of definitive chemoradiotherapy in nonrandomized comparison (16).

In an earlier study, patients treated with surgery alone and radiotherapy alone had 5-year survival rates of 4% and 6%, respectively, with a slight improvement in patient survival (17). A phase II study in Japan found that the 5-year disease-free survival rate of patients with esophageal cancer who received postoperative chemotherapy was better than that of the simple surgery group (55% *vs.* 45%, P=0.037),

and the overall survival rate was also better than that of the simple surgery group (61% *vs.* 52%, P=0.13) (18). In a similar study in France, the disease-free survival rate in the combined chemotherapy group after surgery was 34%, while that in the simple surgery group was 19% (P=0.003), while the 5-year survival rates were 38% and 24%, respectively (P=0.02) (19). In a German experiment published in 2005 (n=189), the 2-year progression-free survival rate of patients undergoing surgery was higher than that of patients undergoing continuous chemoradiotherapy (64% *vs.* 40%, P=0.03) (20).

However, for each patient with esophageal cancer, the effectiveness of treatment is affected by stage, tumor location, treatment, and patient's situation. Therefore, in this study, the independent risk factors for survival and prognosis of patients with T1 thoracic esophageal cancer were studied through the statistics of the data in the Surveillance, Epidemiology, and End Results (SEER) database, and the effect of multi-modal treatment of esophageal cancer was analyzed, to provide more appropriate treatment and improve the survival for patients with T1 thoracic esophageal cancer. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-308/rc).

Methods

Study design

This population-based retrospective cohort study analyzed the data obtained from the SEER database, of 2,027 patients diagnosed with T1 esophageal cancer from 2010 to 2016. The flow diagram of this study is shown in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Sources

The SEER database was established in 1973 and funded by the National Cancer Institute. It is used to record the patients' demographics (race, sex, age, and marital status), tumor characteristics (pathological type, differentiation degree, and histological type), tumor pathology, treatment (i.e., surgery, radiotherapy, and chemotherapy), prognosis (overall survival rate, disease-specific mortality rate, and cause of death), and other information. The version used in this study was SEER 18 Regs Custom Data (with additional

treatment fields), Nov 2018 Sub (1975–2016 varying).

Inclusion and exclusion criteria

The data of the following patients were obtained from the SEER database: (I) patients aged 20–84 years; (II) patients who were diagnosed between 2010 and 2016; and (III) patients with esophageal cancer, specifically a single primary cancer.

The exclusion criteria for this study were as follows: (I) race variables were unknown; (II) sex was unknown; (III) the histological grade of the case was unknown; (IV) the location of the disease was not thoracic (thoracic location: C15.3-upper third of the esophagus, C15.4-middle third of the esophagus, C15.5-lower third of the esophagus); (V) the operative number was 99 (indicating that it was unknown if surgery was performed; death certificate only); (VI) survival times were unknown and 0; (VII) the marital status was unknown; (VIII) the American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) stage was not T1 (T1, T1a, T1b, T1NOS); (IX) the regional lymph nodes were NX, NA, and blank(s); (X) the distant metastatic status was NA and blank(s); and (XI) radiotherapy was recommended, but it was unknown if it was administered. A detailed screening flowchart is presented in *Figure 2*.

Classification and selection of risk factors

According to the SEER database records, the race was classified into white, black, and others (American Indian/ AK Native, Asian/Pacific Islander); sex was categorized into male and female; and the marital status was classified into married (including common law) and single (never married), divorced, widowed, separated, unmarried, or having a domestic partner. In terms of tumor classification, this study used the 7th edition of the AJCC TNM staging system: the N stage was categorized into N0, N1, N2, and N3; M stage was classified into M0 and M1; and the histopathological grade was 4, which was further categorized into well-differentiated (Grade I), moderately differentiated (Grade II), poorly differentiated (Grade III), and undifferentiated (undifferentiated; anaplastic; Grade IV). The primary site was classified into upper one-third (C15.3-upper third of the esophagus), middle one-third (C15.4-middle third of the esophagus), and lower one-third (C15.5-lower third of the esophagus) of the esophagus. The pathological types were classified into squamous cell carcinoma (morphology codes: 8000-8046, 8051-8131, 8148-8157, 8230-8249, 8508, 8510-

8513, 8560-8570, 8575, 8950, 8980-8981), adenocarcinoma (morphology codes: 8050, 8140-8147, 8160-8162, 8170-8175, 8180-8221, 8250-8507, 8514-8551, 8571-8574, 8576, 8940-8941), and others (morphology code: 8936). Patients were divided into the surgical and non-surgical groups according to whether they had undergone surgery or not.

Statistical methods

Statistical analysis was performed using the R language (R-3.6.1). The propensity score matching (PSM) of nearest neighbor matching method was used to reduce the selection bias between groups. The classification data are expressed as medians and percentiles. A Chi-square test and t-test were used to compare the categorical (ordinal) and continuous variables of patients, tumors, and treatment regimens between the non-surgical and surgical groups, and the data were reported as counts (percentages) and mean ± standard deviation, respectively.

The survival curves were drawn using the Kaplan-Meier method and tested using the log-rank test. Cox's regression model was used to analyze the independent risk factors for the prognosis of patients with T1 thoracic esophageal cancer. P<0.05 was considered to indicate statistical significance.

Results

Epidemiological characteristics of the patients

A total of 2,027 cases were included in this study. The average age of patients within the surgical and non-surgical groups was 65 (range, 58–71) and 66 years (range, 58–73 years), respectively. The races of the eligible patients were white (86.09%), black (9.08%), and others (4.83%). The proportions of men and women were 17.27% and 82.73%, respectively. The proportions of married and single people (including divorced, among others) were 60.63% and 39.37%, respectively.

The primary site was the lower one-third of the esophagus, accounting for 77.11% of the total cases. The main pathological types were adenocarcinoma and squamous cell carcinoma, accounting for 27.78% and 72.13% of all cases, respectively. Regarding the histological grade, the proportions of well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated carcinomas were 10.16%, 44.45%, 44.01%, and 1.38%, respectively. *Table 1* shows the details of the characteristics
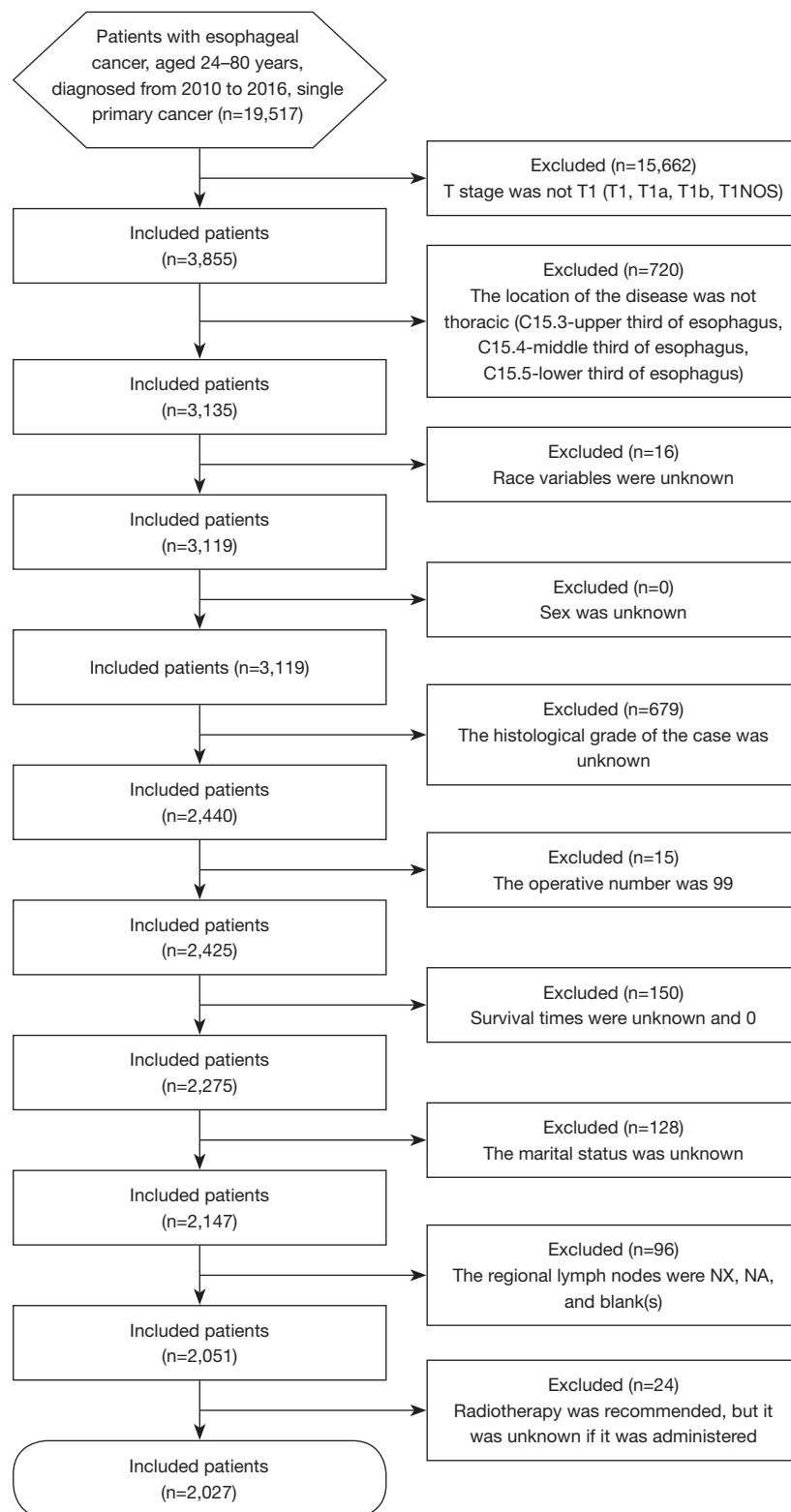
Figure 2 Data filtering process. NX, unknown; regional lymph nodes not stated; regional lymph node(s) cannot be assessed; not documented in patient record. NA, not available.

Table 1 Characteristics of patients with esophageal cancer

Characteristic	Case, n (%)	Non-surgical group 0 (n=1,203)	Surgical group 1 (n=824)	P value
Race, n (%)				<0.001
White	1,745 (86.09)	996 (82.79)	749 (90.9)	
Black	184 (9.08)	144 (11.97)	40 (4.85)	
Other	98 (4.83)	63 (5.24)	35 (4.25)	
Sex, n (%)				0.006
Female	1,677 (82.73)	972 (80.8)	705 (85.56)	
Male	350 (17.27)	231 (19.2)	119 (14.44)	
Age (years), median (IQR)	65 (58, 72)	66 (58, 73)	65 (58, 71)	0.056
YD, n (%)				0.624
2010	352 (17.37)	211 (17.54)	141 (17.11)	
2011	313 (15.44)	197 (16.38)	116 (14.08)	
2012	310 (15.29)	184 (15.3)	126 (15.29)	
2013	361 (17.81)	215 (17.87)	146 (17.72)	
2014	337 (16.63)	198 (16.46)	139 (16.87)	
2015	354 (17.46)	198 (16.46)	156 (18.93)	
Grade, n (%)				<0.001
1	206 (10.16)	55 (4.57)	151 (18.33)	
2	901 (44.45)	483 (40.15)	418 (50.73)	
3	892 (44.01)	649 (53.95)	243 (29.49)	
4	28 (1.38)	16 (1.33)	12 (1.46)	
Histologic, n (%)				<0.001
1	563 (27.78)	441 (36.66)	122 (14.81)	
2	1,462 (72.13)	762 (63.34)	700 (84.95)	
3	2 (0.1)	0 (0.00)	2 (0.24)	
Site, n (%)				<0.001
1	99 (4.88)	84 (6.98)	15 (1.82)	
2	365 (18.01)	253 (21.03)	112 (13.59)	
3	1,563 (77.11)	866 (71.99)	697 (84.59)	
Marital, n (%)				<0.001
Married	1,229 (60.63)	662 (55.03)	567 (68.81)	
Single	798 (39.37)	541 (44.97)	257 (31.19)	
N 7th, n (%)				<0.001
0	1,260 (62.16)	587 (48.79)	673 (81.67)	
1	661 (32.61)	532 (44.22)	129 (15.66)	
2	78 (3.85)	58 (4.82)	20 (2.43)	
3	28 (1.38)	26 (2.16)	2 (0.24)	

Table 1 (*continued*)

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Characteristic	Case, n (%)	Non-surgical group 0 (n=1,203)	Surgical group 1 (n=824)	P value
M 7th, n (%)				<0.001
0	1,408 (69.46)	604 (50.21)	804 (97.57)	
1	619 (30.54)	599 (49.79)	20 (2.43)	
Radiation, n (%)				<0.001
Yes	1,148 (56.64)	554 (46.05)	594 (72.09)	
No	879 (43.36)	649 (53.95)	230 (27.91)	
Chemotherapy, n (%)				<0.001
Yes	930 (45.88)	372 (30.92)	558 (67.72)	
No	1,097 (54.12)	831 (69.08)	266 (32.28)	

Categorical and continuous variables reported as counts (percentages) and mean ± standard deviation, respectively. IQR, interquartile range; YD, year of diagnosis.
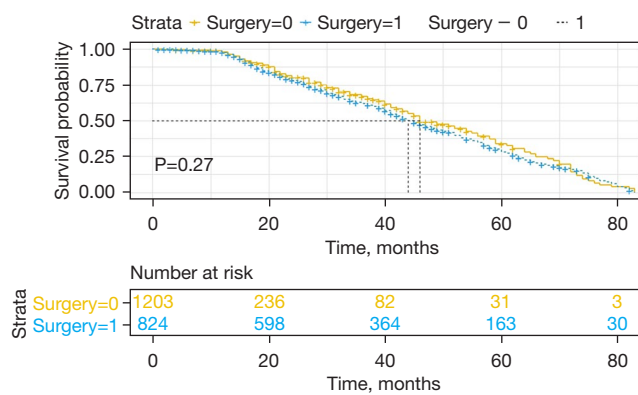
Figure 3 Survival curve (0: non-operation group; 1: operation group).

of patients with esophageal cancer.

Kaplan-Meier survival analysis

The 3- and 5-year survival rates of the non-surgical group were 66.75% and 33.14%, respectively, whereas those of the surgical group were 61.94% and 27.9%, respectively.

The median survival time was 44 months (range, 42–47 months) and 46 months (range, 43–56 months) in the surgical group and non-surgical group (P=0.27), respectively. For patients with T1 thoracic esophageal cancer, there was no significant difference in the values between the surgical and non-surgical groups. The survival curve is shown in *Figure 3*.

Multivariate analysis of prognosis

According to Cox's regression analysis, the results showed that radiotherapy (hazard ratio, 1.46; 95% confidence interval, 1.10–1.93; P=0.008) was an independent risk factor affecting the prognosis, as shown in *Table 2*.

The median survival time was 68 months (range, 57–81 months) and 44 months (range, 41–49 months) in the non-radiotherapy and radiotherapy groups, respectively, in the surgery-selected and chemotherapy-treated subgroup. The log-rank test results showed that the P value was 0.00059. For patients with T1 thoracic esophageal cancer, there was a significant difference in the values between the radiotherapy and non-radiotherapy groups. The survival curve is shown in *Figure 4*.

Discussion

Surgery is the main treatment for patients with stage T1 esophageal cancer. The disadvantage of traditional surgery is that the postoperative complication rate is as high as 30% to 50%. Even in larger hospitals, the mortality rate is still 2% to 3%. Through our research, we found that the median survival of the surgical group (44 months) was slightly lower than that of the non-surgical group (46 months). After the log-rank test, the P value was 0.28 (P>0.05) and was not significant. Therefore, there is no difference between surgery alone and no surgery for patients with T1 thoracic esophageal cancer. Whether postoperative complications

Table 2 Multivariate analysis of prognosis in patients with stage T1 esophageal cancer

Factor	Regression coefficient	HR confidence interval	P value
Male	1.13	0.91, 1.39	0.267
Moderately differentiated carcinoma	0.90	0.74, 1.09	0.290
Poorly differentiated carcinoma	0.85	0.68, 1.06	0.143
Undifferentiated carcinoma	1.16	0.56, 2.38	0.687
Adenocarcinoma	0.97	0.77, 1.22	0.780
Other cancers	2.57	0.34, 19.28	0.359
Middle one-third	1.13	0.76, 1.69	0.549
Lower one-third	1.11	0.75, 1.64	0.595
Single	0.99	0.85, 1.17	0.941
N1	0.94	0.75, 1.18	0.606
N2	0.83	0.51, 1.36	0.456
N3	0.00	0.00, Inf	0.985
M1	1.28	0.88, 1.86	0.193
Operation	1.15	0.92, 1.44	0.230
Radiotherapy	1.46	1.10, 1.93	0.008
Chemotherapy	0.77	0.58, 1.03	0.073

HR, hazard ratio.
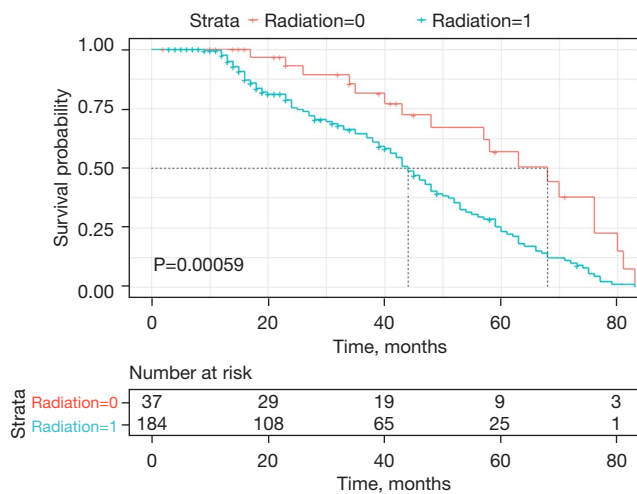
Figure 4 Survival curve of subgroups (0: non-radiotherapy group, 1: radiotherapy group).

are the cause of poor surgical results needs to be studied in the future.

According to COX regression analysis, this study found that race, sex, age, location of onset, or histological type were not independent risk factors for the prognosis of patients with T1 thoracic esophageal cancer. Only radiotherapy was an independent risk factor for the prognosis of patients with T1 thoracic esophageal cancer.

Esophageal cancer is a malignant tumor with a poor prognosis. Multimodal treatments have shown their advantages, but which chemotherapy/radiotherapy regimen is superior is still the subject of large clinical trials. In the subgroup analysis of this study, the median survival time of the non-radiotherapy group was 68 months (range, 57–81 months). The median survival time in the radiotherapy group was 44 months (range, 41–49 months). The log-rank test showed P<0.05. For patients with stage T1 thoracic esophageal cancer, the radiotherapy and non-radiotherapy groups had a significant difference, and the survival of patients was improved. For T1 esophageal cancer patients with surgery and chemotherapy, the absence of radiotherapy is beneficial to improve survival.

The limitations of this study still need to be addressed. First, the SEER database itself has certain limitations as it only includes demographic information, tumor information, treatment information, prognostic information, and other

basic factors that have no influence on esophageal cancer but does not include factors such as smoking, drinking, family history of tumors, or dietary environment, thus causing a bias. Secondly, although the SEER database records information on radiotherapy and chemotherapy, this might cause a bias because the order of radio chemotherapy and surgery treatment was not included in the study. Finally, as this study is a retrospective cohort study, the conclusions cannot be sufficiently validated, and further validation through a prospective cohort study is needed for clinical application.

Conclusions

Our data will be useful for clinicians to formulate a possible basis for the clinical treatment of patients with T1 thoracic esophageal cancer to improve their survival and prognosis.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-308/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-308/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-308/coif). 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).

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