Original Article

Postoperative follow-up strategy based on event dynamics for esophageal squamous cell carcinoma

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Background: Despite the improvements in radical surgery for esophageal squamous cell carcinoma (ESCC), a large number of patients still develop recurrence. This research sought to graphically depict patterns in ESCC recurrence following curative surgical treatment using event dynamics and clarify approaches to postsurgical follow-up on the basis of recurrence time.

Methods: This study included 717 individuals with ESCC who received radical surgery in the Thoracic Department at Fujian Medical University Union Hospital between 2013 and 2016. Event dynamics analysis was performed on the basis of hazard rates. An initial event was defined as the occurrence of local recurrence, distant metastasis, or both.

Results: After complete resection, patients were followed up for a median of 44 months (range, 2–83 months). A total of 223 (31.1%) patients developed recurrence, including 122 (17.0%) patients who developed only locoregional recurrence, and 101 (14.1%) patients who developed only distant metastasis or both locoregional recurrence and distant metastasis. Recurrences were concentrated mainly (98.2%) in the first 4 years of follow-up among all recurrences, with 100 cases (44.8%) in the first year, 69 cases (30.9%) in the second year, and 50 cases (22.4%) in the third and fourth years.

Conclusions: After curative surgery in a multimodal setting, a significant number of patients still experienced recurrence within 4 years after surgery, which suggests that current postoperative esophageal cancer follow-up strategies may need to be modified.

Keywords: Esophageal squamous cell carcinoma (ESCC); surgery; hazard; follow-up strategy; recurrence dynamics

Submitted Mar 01, 2021. Accepted for publication Apr 24, 2021.
doi: 10.21037/atm-21-1373
View this article at: http://dx.doi.org/10.21037/atm-21-1373

Introduction

Esophageal carcinoma has the third highest incidence and the fourth highest mortality rate of all cancers in China (1). Unfortunately, despite significant progress in the comprehensive treatment of esophageal cancer (EC) in recent years, the overall 5-year survival rates rarely exceed 40% (2,3). The primary reason for the poor prognosis is that recurrence develops in most patients, even those who receive treatment with curative intent, suggesting that in many cases, the disease may have already disseminated

at the time of diagnosis. Regular and effective follow-up after optimal treatment is recognized to be a significant part of comprehensive cancer treatment, potentially taking earlier detection and better management of recurrence into account (4).

Multiple statistical methods, including cumulative incidence curves and median intervals, have been used to analyze the postoperative recurrence risks in populations of patients (4,5). Unfortunately, these methods could not offer insight into time-associated changes in the probability of events directly; however, the calculation of event-specific hazard rates during patient follow-up allows for the estimation of such changes (6). So far, only a few studies have focused on the timing of recurrence following operative treatment in patients with esophageal squamous cell carcinoma (ESCC) (7,8), and optimal postoperative surveillance strategies need to be established. Previous studies have shown that in approximately 80% of cases, tumor recurrence occurs within the first 2 years postoperatively. In our study, recurrence was found in 75.7% of patients in the first 2 years after surgery, and the vast majority (98.2%) of patients experienced recurrence 4 years after surgery. We visualized the risk of recurrence of esophageal cancer at various stages after surgery using a risk curve diagram.

This clinical study aimed to focus on recurrence patterns after surgery for ESCC using event dynamics and to confirm the postoperative follow-up strategy according to the times of recurrence.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-21-1373).

Methods

Patients

Clinical and follow-up data of individuals with pT1–4a N0–3, M0 (pathological tumor-node-metastasis stage) (American Joint Committee on Cancer, 8th edition) thoracic ESCC who were treated with radical surgery in the Thoracic Department at Fujian Medical University Union Hospital between 2013 and 2016. The study participants each had a definitive diagnosis of a single primary tumor, and they all received radical (R0) surgical treatment to resect the tumor with 2- or 3-field lymph node (LN) dissection. Participants were aged between 18 and 75, and the pathological type was squamous cell carcinoma. The exclusion criterion was cases in which patient death occurred in the time immediately following the operation (in the 30 days after the procedure or during the initial hospital stay).

Chest and abdominal CT examinations were used for routine preoperative staging. To exclude possible distant metastases, nuclear medicine scans of bone and brain MRI or CT examinations were performed. Positron emission tomography (PET) was performed for disease staging during the study period. Neoadjuvant treatment was administered when the preoperative examination suggested a locally advanced tumor. Neoadjuvant chemotherapy routinely consisted of cisplatin (75 mg/m^2 on day 1; completion of a minimum of 2 cycles, each lasting 21 days). Adjuvant chemoradiotherapy following surgery consisted of cisplatin (75 mg/m^2 on day 1; completion of a minimum of 2 cycles, each lasting 21 days).

Surgery

Prior to surgery, each patient was subjected to intubation using a common single lumen tube with no bronchial blocker and then maneuvered into a semi-prone position. Many of the study participants underwent radical esophageal cancer resection comprising right thoracotomy with 2-field LN dissection. and gastric tube reconstruction. In each case, 2-field LN dissection was carried out under normal conditions; based on the findings of frozen section examination of LNs along the right recurrent laryngeal nerve or presurgical images, cervical nodes were also dissected (9).

Follow-up

At 4 weeks after surgery, patients underwent their first routine follow-up examinations. Over the next 2 years, follow-ups were held every 3 months, and after that, every 6 months. During the time they were followed up, patients were monitored through examinations, including annual neck, thoracic, and abdominal CT, and neck and abdominal ultrasonography (US). Head-enhanced MRI, positron emission tomography, and bone scintigraphy were performed based on clinical symptoms, clinical signs, and chemical analysis results. Overall survival (OS) was considered as the period between the operation date and the date of death or final follow-up. Recurrent cases were diagnosed based on physical examination and diagnostic imaging results, and if necessary, pathological examination of biopsy specimens was used to confirm recurrence. Local-

regional recurrent disease was considered when cancer reappeared at the surgical margin, ipsilateral hilum, or mediastinum, and all other sites of failure were defined as distant metastasis. Disease-free survival (DFS) was considered as the period between the operation date and the date of recurrence diagnosis or last follow-up. Only first events were considered in this study.

Statistical analysis

For the evaluation and comparison of the primary outcomes (OS and DFS), Kaplan–Meier curve analysis and the log-rank test were employed, respectively. Event dynamics were examined through estimation of the discrete hazard rate of a considered event using the life-table method (i.e., the conditional probability that an event would occur during a time period, considering the patient had not experienced it at the beginning of the period). Since, due to random variation, the estimated hazard rates were found to be unstable to a certain degree, a kernel-like smoothing procedure was adopted, and a graphical representation of the smooth curve was created to allow the underlying pattern to be better understood (6). We performed discretization of the time axis in 2-month units, and the measurement of all-hazard rate levels was carried out as 'events/patients at risk per 2-month interval'. Potential covariates were age, sex, pathological stage, and histological type. For the modelling of each variable's time dependence, natural cubic splines were applied, with internal knots spaced equal distances apart within the month range (0–60 months). For all statistical procedures, $P < 0.05$ was considered to indicate statistical significance. SPSS version 22.0 (IBM Corp., Armonk, NY) was used for all data analyses in this study.

Approval for this single-institution, retrospective study was granted by the institutional review board of Fujian Medical University Union Hospital. All procedures performed in this study involving human participants adhered to the Declaration of Helsinki (as revised in 2013). The requirement for individual consent for this analysis was waived due to its retrospective nature.

Results

Table 1 presents the characteristics of the 717 thoracic ESCC patients included in this study. The median age of the 717 patients was 59 (range, 34–75) years, with a male-to-female ratio of 3.1:1. The most frequent tumor localization was the middle esophageal third (57.2% of all cases); the most frequent tumor differentiation grade was G2 (48.5%); and the most frequent tumor stage was stage III (38.2%). The most frequent tumor infiltration category, pT3, was confirmed in 51.3% of all cases, and was followed by pN0 in 50.9% of cases. Almost all patients (95.5%) underwent thoracoscopic surgery, and 566 (78.9%) patients were treated with 2-field lymphadenectomy. Seventy-four patients (10.3%) underwent neoadjuvant treatment, and 348 (48.5%) received postoperative adjuvant therapy.

After complete resection, the patients were followed up for a median of 44 (range, 2–83) months. A total of 223 (31.1%) patients developed recurrence, including 122 (17.0%) patients who developed only locoregional recurrence and 101 (14.1%) patients who developed only distant metastasis or both locoregional recurrence and distant metastasis. *Figure 1* shows the time of recurrence after radical esophagectomy for all 223 patients who developed recurrence. Recurrences were concentrated mainly (98.2%) in the first 4 years of follow-up among all recurrences, with 100 cases (44.8%) in the first year, 69 cases (30.9%) in the second year, and 50 cases (22.4%) in the third and fourth years.

Firstly, an analysis was conducted of the hazard rate of comprehensive therapy failure in the entire cohort. Recurrence patterns based on event dynamics are shown in *Figure 2*. The recurrence risk rate curve showed a peak at 12 months postoperatively, followed by a gradual decline until another small peak of recurrence at 36–40 months. The risk rate of recurrence dropped to a very low level 4 years after surgery.

The risk rate curve for local recurrence was similar to the overall recurrence risk rate curve (*Figure 3*). However, the risk rate for local recurrence was lower, and dropped to a very low level 2 years after surgery. On the other hand, the hazard rate curve for distant metastasis or both locoregional recurrence and distant metastasis showed a double-peak pattern curve (*Figure 4*), with the first maximum peak occurring at 16–20 months postoperatively. A small peak was observed at 42 months after surgery.

As for the pathological stage, the hazard rate curves' peaks displayed increasing height with increasing pathological T and N stages (*Figure 5*). For both T3 and T4a patients, we observed a maximum peak that appeared approximately 9 months postoperatively, followed by a sharp decrease in the risk of recurrence in T4a patients and a small peak at approximately 42 months postoperatively in T3 patients. The first peak of the postoperative recurrence risk

Table 1 Characteristics of 717 thoracic ESCC patients included in the study

Variable	No. of patients (%)
Age, years	
Median	59
Range	34–75
Gender	
Male	543 (75.7)
Female	174 (24.3)
Surgical approach	
VATS	685 (95.5)
Open surgery	32 (4.5)
Range of lymph node dissection	
Mediastinal + abdominal	566 (78.9)
Mediastinal + abdominal + cervical	151 (21.1)
Tumor location	
Upper third	65 (9.1)
Middle third	410 (57.2)
Lower third	242 (33.8)
Pathologic T category	
1	187 (26.1)
2	122 (17.0)
3	368 (51.3)
4a	40 (5.6)
Pathologic N category	
0	365 (50.9)
1	191 (26.6)
2	122 (17.0)
3	39 (5.4)
Pathologic TNM stage	
I	178 (24.8)
II	203 (28.3)
III	274 (38.2)
IV	62 (8.6)
Differentiation	
Well (G1)	266 (37.1)
Moderate (G2)	348 (48.5)
Poor (G3)	103 (14.4)
Neoadjuvant therapy	
None	643 (89.7)
Chemotherapy	55 (7.7)
Chemoradiotherapy	19 (2.6)
Adjuvant therapy	
None	369 (51.5)
Chemotherapy	313 (43.7)
Chemoradiotherapy	35 (4.9)
Postoperative complications	
Anastomotic fistula	
Yes	67 (9.3)
No	650 (90.7)
Pulmonary infection	
Yes	154 (21.5)
No	563 (78.5)
Chylothorax	
Yes	16 (2.2)
No	701 (97.8)
Recurrence	223 (31.1)
Local-regional recurrence	122 (17.0)
Distant metastasis	101 (14.1)

ESCC, esophageal squamous cell carcinoma; VATS, video-assisted thoracic surgery.

curve for pT2 patients occurred 18 months after surgery, approximately 9 months later than the curve for pT3 and pT4a patients. The risk curve for postoperative recurrence in pT1 patients was at a very low level, similar to that in pN0 patients. The peak risk of postoperative recurrence in pN3 patients occurred at 9–10 months postoperatively, whereas in pN1 and pN2 patients, the risk of recurrence peaked at approximately 12 months postoperatively. Also, there was a small peak in recurrence among pN2 patients at approximately 36 months postoperatively.

Discussion

Postoperative recurrence of EC is high and significantly affects the prognosis of patients undergoing curative

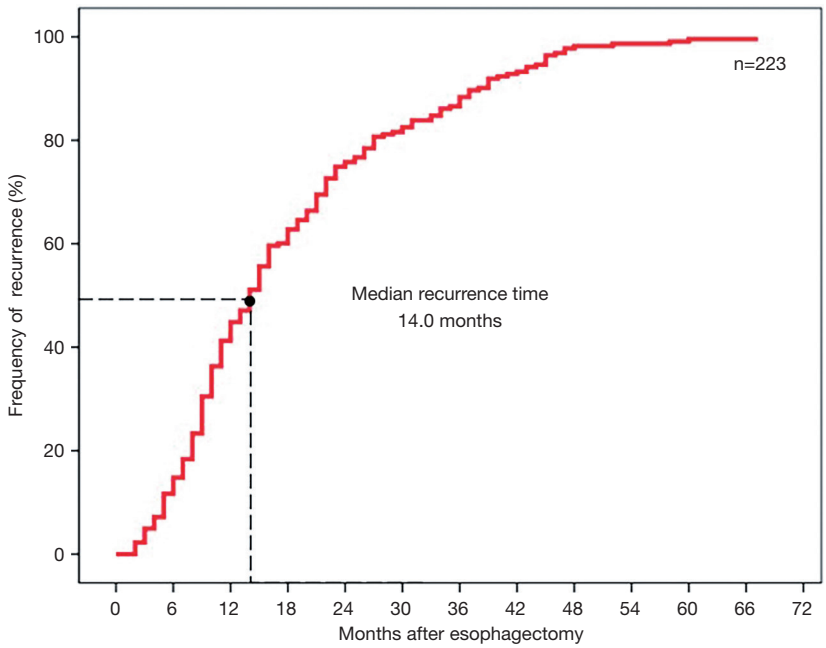

Figure 1 Times of recurrence after radical resection in 223 patients with esophageal squamous cell carcinoma.

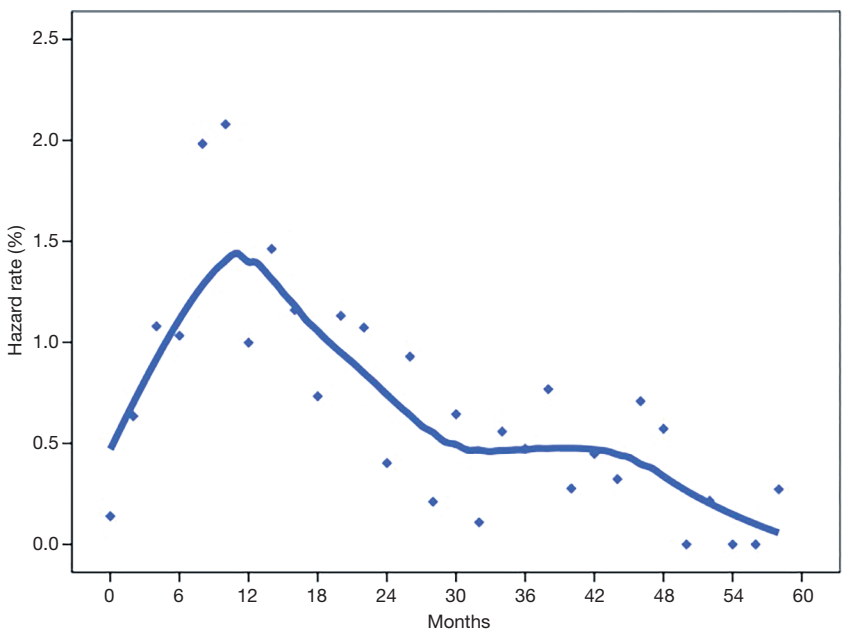

Figure 2 Hazard rate curve for recurrence in 717 patients with esophageal squamous cell carcinoma after radical esophagectomy.

treatment (7,10,11). Several studies (12-15) have shown that further treatment, including surgical resection, chemotherapy, and radiation therapy, can significantly improve survival outcomes for patients with recurrent metastases after EC surgery. Yamashita *et al.* (13) analyzed 290 patients who underwent radical surgery for EC and concluded that although the prognosis for recurrent EC remains poor, it can be improved with effective combination therapy, including local therapy, especially in patients with LNs or lung recurrence. Hiyoshi *et al.* (14) also showed that

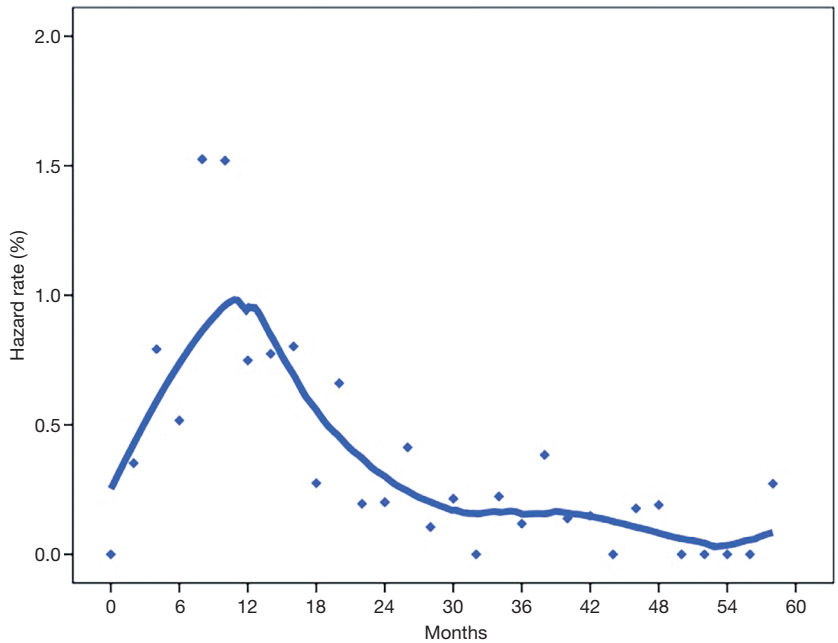

Figure 3 Hazard rate curve for locoregional recurrence in 717 patients with esophageal squamous cell carcinoma after radical esophagectomy.

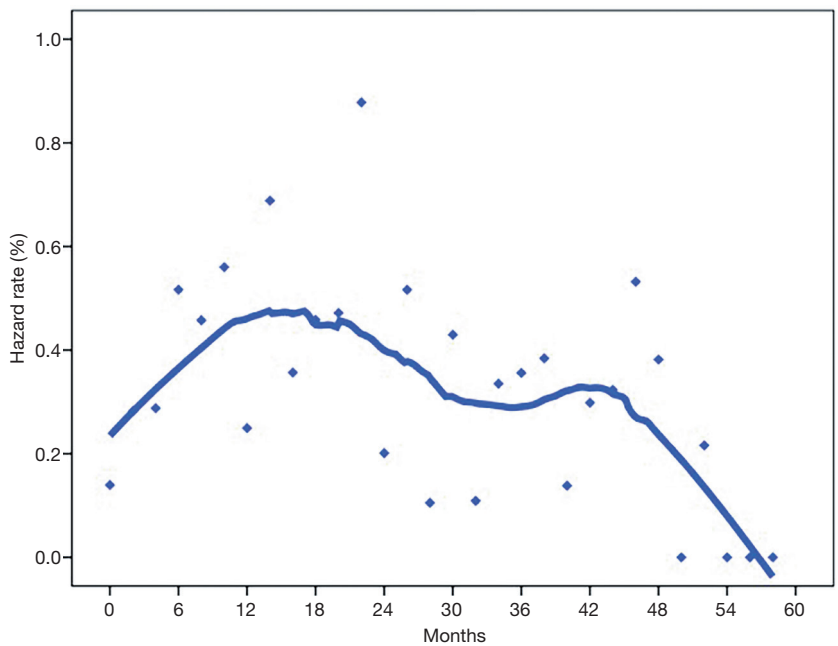

Figure 4 Hazard rate curve for distant metastasis or both locoregional recurrence and distant metastasis in 717 patients with esophageal squamous cell carcinoma after radical esophagectomy.

multimodal therapy provides significant benefits to patients with recurrent EC after esophagectomy. When recurrent lesions are isolated or limited, aggressive surgery should be incorporated into the treatment strategy.

Among patients with recurrence, some cases can be treated even after the recurrence is detected, while others

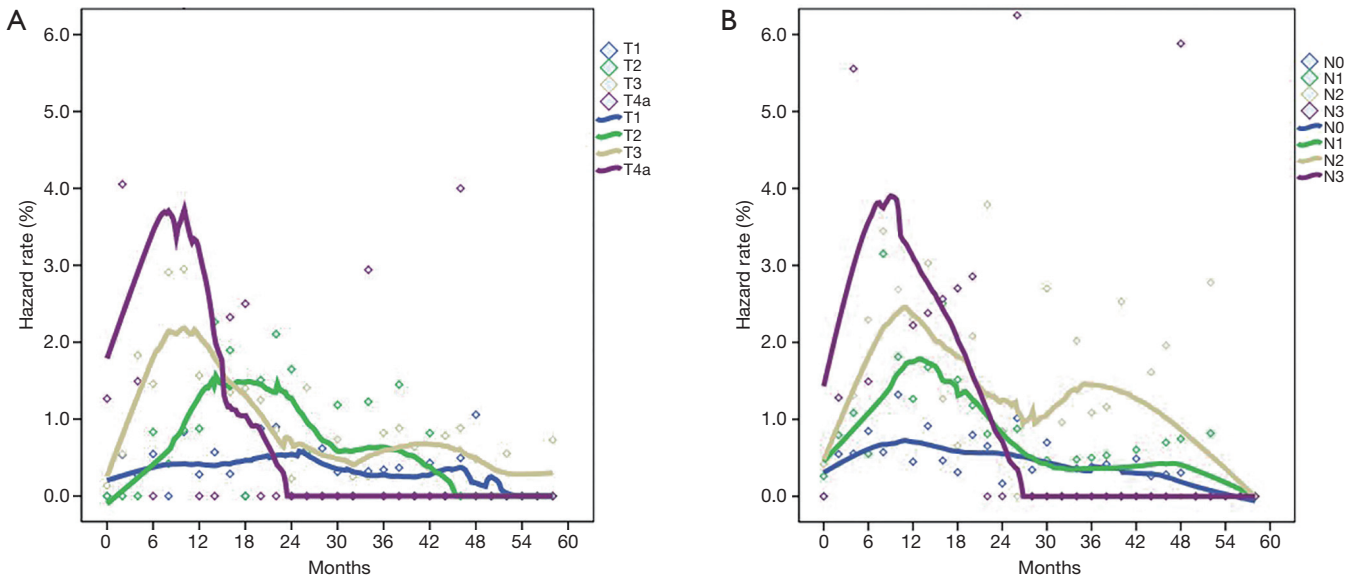

Figure 5 Hazard rate curve for recurrence in 717 patients with esophageal squamous cell carcinoma according to (A) the pathological T category and (B) the pathological N category after radical esophagectomy.

cannot due to the severity of tumor progression (14,15). To some extent, this suggests that current postoperative follow-up strategies for EC may not be sensible. In some patients, early postoperative recurrent metastases are not promptly diagnosed and treated, thus causing them to miss the optimal treatment opportunity. In short, an effective follow-up strategy is critical for transitioning the health care system to a value-based system, and individually designed follow-up strategies are required for ESCC.

Each thoracic surgery institution has its own strategy for postoperative follow-up monitoring of patients with EC. At our institution, we generally recommend that patients be examined every 3 months for the first 2 years after surgery, and then every 6 months after that for asymptomatic patients. On the basis of the National Comprehensive Cancer Network (NCCN) guidelines (16), asymptomatic patients should routinely undergo examination every 3 months for 2 years, and then every 6 to 12 months after that. However, our study suggests that this frequency of follow-up may be inadequate. In the present study, recurrence was found in 75.7% of patients in the first 2 years after surgery, and the vast majority (98.2%) of patients experienced recurrence 4 years after surgery. As surgical techniques and treatments have improved, the prognosis of EC patients has become more favorable, and it is important to recognize that this may have also changed the recurrence patterns of EC. Based on our study results, an appropriate increase in the frequency of examinations in EC patients during the first 4 years after surgery should be considered.

In approximately 80% of ESCC cases, tumor recurrence occurs within the first 2 years postoperatively (17,18), which means that a significant number (approximately 20%) of patients experience recurrence after this time. Steffen *et al.* showed that patients with adenocarcinoma rarely relapsed after 3 years of event-free survival, but those with squamous cell cancer remained at risk of recurrence 4 years after surgery (7). These previous studies also indicate, in part, that modification of postoperative EC follow-up strategies is needed.

As a retrospective study, the results of this study will need to be further validated by future large prospective studies. However, this study has highlighted that in EC, a disease with a high recurrence rate, current postoperative follow-up strategies may need to be adapted to detect and treat recurrence at an early stage.

Acknowledgments

Funding: The study was supported by Climbing project of Science and Technology Department of Fujian Province (2018Y9058), Fujian Provincial Joint Research Project of Health Care and Education (WKJ2016-2-09), Key

programs of Science and Technology Department of Fujian Province (2014Y0101), Fujian Key Laboratory of Cardio Thoracic Surgery (Fujian Medical University).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-21-1373

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-21-1373

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-1373). 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. This single-institution, retrospective study was approved by the institutional review board of Fujian Medical University Union Hospital. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

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(English Language Editor: A. Kassem)

Cite this article as: Zhang Y, Chen M, Xiao J, Liang M, Zheng W, Chen C, Zheng B. Postoperative follow-up strategy based on event dynamics for esophageal squamous cell carcinoma. Ann Transl Med 2021;9(8):699. doi: 10.21037/atm-21-1373