Clinical Impact of the Interval Between Chemoradiotherapy and Esophagectomy in Esophageal Squamous Cell Carcinoma Patients

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Background. **The optimal interval between chemoradiotherapy (CRT) and esophagectomy in patients with esophageal squamous cell carcinoma is still undetermined. The aim of this study was to evaluate the association between different treatment intervals and clinical impact, including perioperative outcome and long-term survival.**

Methods. **We retrospectively reviewed data from 665 patients with esophageal squamous cell carcinoma who underwent CRT and esophagectomy between 2008 and 2011 in Taiwan. Based on the interval between CRT and esophagectomy, patients were divided into group 1, less than 30 days; group 2, 30 to 59 days; group 3, 60 to 89 days; or group 4, 90 days or more. The impact of the treatment interval on perioperative outcomes and overall survival were assessed. A Cox regression model was used to identify prognostic factors for overall survival.**

Results. **There were 90 patients in group 1, 385 patients in group 2, 141 patients in group 3, and 49 patients in group 4. The 30-day surgical mortality rate was 5.6%, 2.9%, 1.4%, and 10.2% for groups 1, 2, 3, and 4, respectively ($p = 0.018$). The 90-day surgical mortality rate was 12.2%, 6.8%, 5.7%, and 18.4% for groups 1, 2, 3, and 4, respectively ($p = 0.012$). The differences between surgical margin positivity rates were also significant: 2.2% in group 1, 4.9% in group 2, 9.2% in group 3, and 12.2% in group 4 ($p = 0.032$). The treatment interval was not associated with the complete response and the overall survival.**

Conclusions. **Although early operation (less than 30 days) is associated with reduced rates of surgical margin positivity, the potential benefits appear to be outweighed by the significant increase in postoperative mortality. The surgical timing that optimizes both mortality and surgical margin positivity requires further study.**

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Esophageal squamous cell carcinoma (ESCC) is one of the most aggressive malignancies worldwide. The majority of patients die within 1 year of diagnosis, and the 5-year overall survival (OS) rate is less than 20% [1, 2]. In Taiwan, esophageal cancer is the sixth most common cancer among males, and the histologic type diagnosed in most patients is advanced squamous cell carcinoma [2]. The most appropriate treatment modality for local advanced ESCC is still undetermined, and the outcome for patients with ESCC is still poor, regardless of chemoradiotherapy (CRT) or surgical management.

According to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for esophageal cancer [3], neoadjuvant CRT is recommended for patients with clinical T2 to T4a, N0 to N+, and M0 disease. Neoadjuvant CRT may reduce the tumor burden, increase the complete resection rate, and prolong OS. A large randomized trial indicated that preoperative CRT improved survival among patients with potentially curable esophageal cancer [4]. Recent metaanalyses also concluded that, for the treatment of locally advanced esophageal carcinoma, the addition of neoadjuvant CRT leads to a survival benefit compared with surgery alone [5–7]. However, most clinical trials stipulated that esophagectomy should be performed within 4 to

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8 weeks after neoadjuvant CRT. The interval between neoadjuvant CRT and esophagectomy has not been adequately investigated in these randomized trials. Previously, four retrospective analyses focused on the treatment interval between neoadjuvant CRT and surgery [8–11]. Their results were inconsistent, and the optimal timing for surgery is still controversial.

The aim of this study was to investigate the relationship between the treatment interval and the clinical impact in a large series of patients with ESCC. The clinical impact included surgical mortality, freedom from surgical margin positivity, and long-term survival.

Material and Methods

The Institutional Review Board of Chang-Hua Christian Hospital approved this study and granted a waiver of the informed consent process. A retrospective cohort design was used by linking individual patient-level data with encrypted personal identification numbers from computerized data of the Taiwan cancer database and the National Registry of Deaths database. The Taiwan Cancer Registry records detailed clinical information about patients diagnosed with cancer in Taiwan. The database contains medical information, including demographic characteristics (sex, date of birth, residence), cancer identification (date of diagnosis, primary site, laterality, histology, behavior, grade/differentiation, diagnostic confirmation, tumor size, regional lymph nodes examined, and so forth), stage of disease at initial diagnosis (clinical TNM, clinical stage, pathologic TNM, pathologic stage), first course of treatment (date of first course of treatment, date of first surgical procedure, surgical procedure, surgical margin, date radiotherapy started and ended), radiotherapy doses, chemotherapy, date chemotherapy started), follow-up (recurrence, date of last contact or death), and administration (care facilities). The types of CRT and the details of surgical sections (such as extent of the lymph node dissection) were not included in the database.

In Taiwan, the national insurance covered all the preoperative examinations, including complete blood count, serum biochemistry tests, computed tomography scan of the chest and upper abdomen, endoscopic ultrasonography, and positron emission tomography–computed tomography. Physicians judged clinical stages according to these examinations.

This study used nationwide data from the Taiwan Cancer Registry between 2008 and 2011. The clinical sample was identified from the pooled database by the International Classification of Diseases–Oncology (ICD-O) site codes C15.0, C15.1, C15.2, C15.3, C15.4, C15.5, C15.8, and C15.9. Squamous cell carcinoma was included for analysis (ICD-O codes 8052, 8070, 8071, 8072, 8073, 8074, 8076, 8077, 8083, and 8044). We identified a total of 6,140 patients with ESCC. The initial treatment modalities included the following: (1) definite CRT (n = 3,020); (2) CRT followed by surgery (n = 776); (3) surgery alone (n = 679); (4) surgery followed by chemotherapy or radiotherapy or both (n = 696); (5) radiotherapy alone (n = 442); (6) chemotherapy alone (n = 333); (7) others (n = 34); and (8) unknown (n = 160). We obtained data to examine how the treatment interval between CRT and esophagectomy influences the clinical outcome in patients with ESCC.

Patients receiving CRT followed by surgery (n = 776) were enrolled. Patients who had distant metastasis in the CRT followed by surgery group were excluded (n = 104), because distant metastasis was a surgical contraindication. Patients receiving esophagectomy more than 180 days after CRT were also excluded (n = 7) because of high possibility of salvage esophagectomy. Therefore, a total of 665 patients with ESCC undergoing CRT and esophagectomy were included in this study.

The interval between CRT and esophagectomy was calculated from the end of radiotherapy to the date of surgery. The patients were divided into four groups, depending on the length of the interval that elapsed between CRT and surgery: group 1, less than 30 days; group 2, 30 to 59 days; group 3, 60 to 89 days; and group 4, 90 days or more. The following items were included in the study: age, sex, treatment interval, TNM classification, radiation dose, histologic grading, tumor location, surgical margin, 30-day surgical mortality, 90-day mortality, and survival rate. The histology was described according to the World Health Organization classification. All the patients were staged according to the seventh edition of the TNM staging system [12]. Both clinical and pathologic stages were based on the seventh edition of the TNM system. We performed multivariate analysis to determine which factors were independently associated with OS.

Statistical Analysis

Overall survival was measured from the date of esophagectomy until all-cause death or the censoring date of December 31, 2012. The date of death was confirmed using the database of death certificates, managed by the Ministry of Health and Welfare in Taiwan (http://www.mohw.gov.tw/). The OS curves were generated using the Kaplan-Meier method and compared using the log rank test, and the crude survival was calculated with the life test method. Comparisons of categorical data between the two groups were made by the χ^2 or Fisher's exact test. Continuous variables were compared by two-tailed t test. To investigate the impact on OS, the following clinicopathological factors were included in the univariate analyses: age, sex, interval, tumor location, histologic grade, surgical margin, TNM classification, and radiation dose. All variables were entered in the multivariate analyses to identify the independent predictors of survival. Univariate and multivariate analyses were performed with the Cox proportional hazards model using SPSS software (version 17.0; SPSS Inc, Chicago, IL). Cox regression (forward conditional) model was used for multivariate survival analysis. Cox survival curves adjusted for age, sex, tumor location, grade, surgical margin, pathologic stage, and radiation dose. Statistical analysis was considered to be significant for a p value less than 0.05.