Re-evaluating the Optimal Radiation Dose for Definitive Chemoradiotherapy for Esophageal Squamous Cell Carcinoma

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Background: The optimal radiation dose for treating esophageal squamous cell carcinoma (ESCC) has long been debated. We evaluated if doses greater than 50.4 Gy delivered with modern techniques are beneficial in terms of tumor control, survival, and toxicity.

Methods: We included 193 consecutive patients with ESCC treated with definitive concurrent chemoradiotherapy from 1998 to 2012. Patients were treated to a dose of ≤50.4 Gy (low-dose, $n = 137$) or greater than 50.4 Gy (high-dose, $n = 56$). Tumor response, local-regional control, survival, and treatment toxicity were compared between groups.

Results: High-dose group had a significantly lower local failure rate (17.9% versus 34.3%, $p = 0.024$) and a marginal better 5-year local-regional failure-free survival (68.7% versus 55.9%, $p = 0.052$) than the low-dose group. No significant differences were found between high- and low-dose groups in tumor complete response rate ($p = 0.975$), regional failure rate ($p = 0.336$), distant metastasis rate ($p = 0.390$), or 5-year overall survival ($p = 0.617$). No difference in the incidence of toxic effects was observed between the two groups except for grade 3 skin reaction (12.5% [high] versus 2.2% [low], $p < 0.001$) and grade greater than or equal to 3 esophageal stricture (32.1% [high] versus 18.2% [low], $p = 0.037$).

Conclusions: Local tumor control might be improved by higher dose of greater than 50.4 Gy, when delivered with modern techniques and concurrent chemotherapy, at the consequence of increased toxicity without impact on overall survival.

Key Words: Esophageal squamous cell carcinoma, Radiation dosage, Chemoradiotherapy.

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Concurrent chemoradiotherapy (CRT) followed by surgery is widely accepted as the standard treatment for locally advanced esophageal cancer.[1,2] With the development of more advanced radiation techniques and chemotherapy regimens, the question has been raised as to whether high-dose radiotherapy given concurrently with effective chemotherapy could achieve similar or better survival rates compared with the standard treatment, especially for esophageal squamous cell carcinoma (ESCC).[3–5] The optimal radiation dose for definitive treatment of ESCC, however, remains in debate, particularly in light of the ability of modern radiation techniques to safely and effectively deliver higher radiation doses.[6–8]

Some groups maintain that a dose of 60 to 70 Gy is needed to control gross ESCC tumors.[9] However, the results of the Radiation Therapy Oncology Group (RTOG) trials 85-01[10] and RTOG 94-05[11] led to the adoption of concurrent CRT to a total dose of 50.4 Gy given in conventional fractions as the standard protocol. Investigators continue to debate the contribution of outdated radiation techniques to these results. Moreover, in RTOG 94-05, the longer treatment time and the lower fluorouracil dose in the high-dose group may also have contributed to the lack of superiority of the high (64.8 Gy) dose over the lower (50.4 Gy) dose in terms of local control and survival.[11–13]

On the contrary, a review of neoadjuvant concurrent CRT trials for esophageal carcinoma showed evidence of a dose-response relationship between increasing radiation dose and pathologic complete response (pCR) rate in a dose range of 20 to 60 Gy.[14] A retrospective study also revealed that patients with stage II to III esophageal cancer treated with concurrent CRT with a radiation dose greater than 51 Gy (54–64.8 Gy) had better local-regional control and survival than did those treated with a lower dose (≤51 Gy).[12] Other studies found that doses of 50 to 65 Gy given concurrently with chemotherapy may improve local control and overall survival (OS) relative to low-dose radiation (≤50 Gy) for cervical and upper thoracic esophageal carcinoma.[15,16]

Given these discrepancies on the best radiation dose for definitive therapy for ESCC, we retrospectively analyzed 193 ESCC patients who underwent definitive CRT, using modern radiation delivery techniques, at a single institution to determine whether dose escalation above 50.4 Gy is beneficial in terms of tumor control or survival.

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PATIENTS AND METHODS

Patient Selection

All patients had histologically proven primary ESCC. Patients with prior malignancies or severe uncontrolled medical conditions and those who underwent surgery after CRT were excluded, leaving a total of 193 patients with ESCC who received concurrent CRT as definitive therapy from May 1998 through May 2012 for this analysis. Treatment records and hospital charts were reviewed for baseline (pretreatment) and treatment characteristics, toxicity during and after therapy, and tumor control and survival outcomes. This study was approved by the appropriate institutional review board.

Pretreatment Evaluations

Disease in all cases was staged (or restaged) according to the sixth (2002) edition of the American Joint Committee on Cancer (AJCC) staging manual for esophageal carcinoma. Pretreatment evaluations included a medical history and physical examination, upper gastrointestinal double-contrast barium radiography, esophagogastroduodenoscopy (EGD) with endoscopic ultrasonography and biopsy, computed tomography scan of the chest and abdomen, and positron emission tomography (PET) when available. Of the 193 patients, 150 (77.7%) cases were PET-staged.

Treatment Approaches

Radiation had been delivered by three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, or proton beam therapy. The clinical target volume (CTV) included the gross primary tumor volume with a radial margin of 0.5 to 1 cm and a proximal and distal margin of 3 to 4 cm and also covered the regional nodal regions. The nodal CTV was defined by a 0.5- to 1-cm expansion around the nodal gross tumor volume. The planning target volume (PTV) was the CTV plus a uniform 0.5-cm expansion margin. For both the low-dose (≤50.4 Gy) and high-dose (≥54–66 Gy) groups, prescribed dose is given to the PTV. All patients received platin- or taxane-based chemotherapy with fluorouracil, given weekly during the radiotherapy.

Evaluations During and After Therapy

During therapy, symptoms and blood test results were closely monitored and esophagography was done every 2 weeks. Evidence of acute toxicity was assessed weekly during CRT and every 2 weeks for 90 days after the completion of CRT. Clinical response to treatment was evaluated based on the results of EGD, biopsy (when available), computed tomography scan of chest and abdomen, and PET (when available) at 0 to 3 months after the completion of CRT. Patients usually underwent follow-up examinations including EGD and imaging studies every 3 months for the first year and every 6 months thereafter. EGD with biopsy was done when local-regional failure was suspected, and all the local-regional failure was histologically proven.

Outcomes

Tumor response and treatment toxicities were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) system[17] and the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.[18] Complete response on PET was defined as the lack of uptake of fluorodeoxyglucose on the PET scan after treatment.[19] Local/regional failure was defined as the persistence or recurrence of the primary tumor and regional lymph nodes, whereas distant failure was defined as the metastasis to any site beyond the primary tumor and regional lymph nodes. Distant metastasis–free survival (DMFS), local-regional failure-free survival (LRFFS), disease-free survival (DFS), and OS were defined as the time from the end of CRT to tumor metastasis, local-regional tumor persistence or recurrence, the first evidence of any treatment failure, and death from any cause, respectively.

Statistical Analysis

Patients were stratified by the total radiation dose (low-dose group ≤50.4 Gy and high-dose group >50.4 Gy). Statistical analysis was done with SPSS standard version 16.0 (SPSS Inc., Chicago, IL). Fisher's exact texts were used to assess measures of association in frequency tables. DMFS, LRFFS, DFS, and OS were assessed with the Kaplan-Meier method and curves compared with log-rank tests. The Cox regression model was used for multivariate analysis to assess the effect of patient characteristics and other factors on the endpoints. Statistical tests were based on a two-sided significance level, and p values of less than 0.05 were considered significant.

RESULTS

Patient Characteristics

The characteristics of the 193 patients are summarized in Table 1. The radiation dose per fraction ranged from 1.6 to 2.4 Gy, while 90.2% of the radiation treatments were delivered in conventional fractions. Except one case who only received 41.4 Gy/23 F because she refused the last two fractions of treatment for her grade 3 toxicity and good treatment response, all the other patients received a total dose of 45 to 66 Gy. In terms of treatment completion, 97.8% (134) and 98.2% (55) of the low-dose and high-dose groups completed the radiotherapy without any delays longer than 3 days, and 78.1% (107 in low) and 76.8% (43 in high) of the two groups received the planned chemotherapy without dose reduction. Higher radiation doses (>50.4 Gy) were more often delivered to proximal ESCCs by intensity-modulated radiation therapy, whereas the lower doses (≤50.4 Gy) were more often given to middle/distal ESCCs by three-dimensional conformal radiation therapy or proton therapy ($p < 0.001$, Table 1). No significant differences were found between the two groups in other clinicopathologic variables, including general characteristics, receiving induction chemotherapy or not and treatment response ($p > 0.05$, Table 1).

Patterns of Failure

During the median observation period of 32.4 months (range 2.5–161.3 months) for all patients (45.9 months [range 3.6–148 months] for those alive at the time of analysis), 69 experienced local-regional failure, 59 distant metastasis, and 123 death. Of the 69 patients who had local-regional failure

