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Supplemental Appendix for:
Postoperative Radiotherapy in Pathological T2-3N0M0 Thoracic Esophageal Squamous Cell Carcinoma: Interim Report of a Prospective, Phase III, Randomized Controlled Study
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Protocol for

Postoperative Radiotherapy in Pathological T2-3N0M0 Thoracic Esophageal Squamous Cell Carcinoma: Interim Report of a Prospective, Phase III, Randomized Controlled Study

Protocol number: NCT01745107
Protocol title: Phase III Study of Prophylactic Postoperative Intensity-Modulated Radiation Therapy in Stage T2-3N0M0 Disease of Thoracic Esophageal Squamous Cell Carcinoma

Objectives

Primary objective

The primary objective of this study is to determine whether prophylactic intensity-modulated radiation therapy (IMRT) after surgery will improve disease-free survival (DFS) in pathological stage T2-3N0M0 disease of thoracic esophageal squamous cell carcinoma (UICC 7th edition).

Secondary objectives

Determine overall survival rate
Determine recurrence pattern
Safety of postoperative radiotherapy

Background

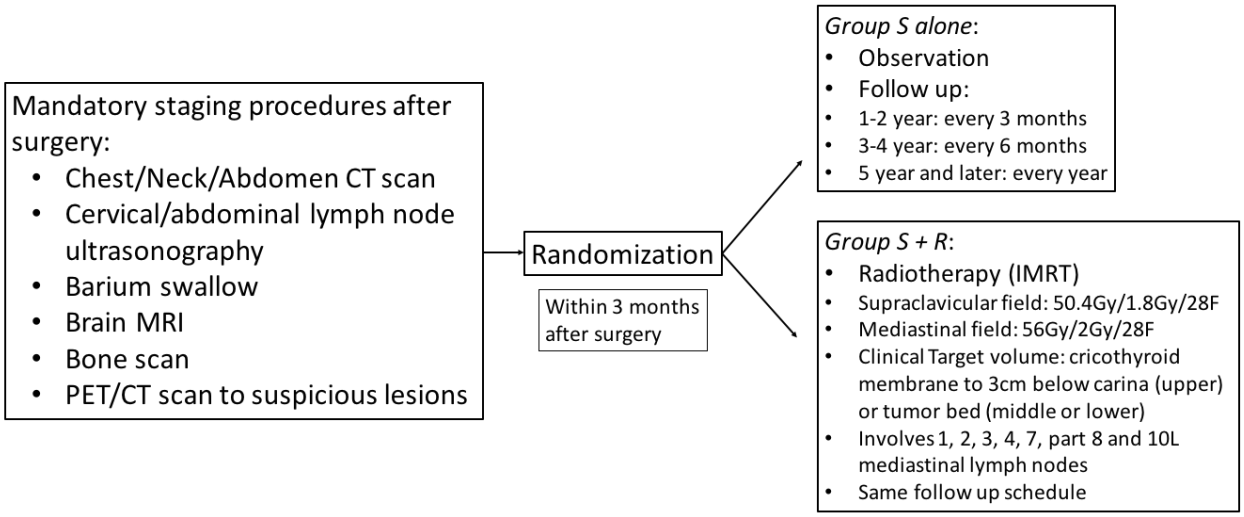
Although preoperative chemoradiation followed by surgery is the most common therapeutic approach for patients with resectable esophageal cancer, considerable number of patients received esophagectomy as their first treatment modality. Accordingly, postoperative treatments have played an important role because of the poor survival rates of the patients who have been treated with resection alone. The existing data shows that the 5-year overall survival rate of pathological stage T2-3N0M0 (UICC 7th edition) of thoracic esophageal squamous cell carcinoma(TESCC) after surgery is about 50%, and local-regional lymph nodes metastases is responsible for the major cause of failure while distal metastases account for relatively less ratio. Therefore, the subclinical residual tumor is affirmative even if the early disease underwent curable excision and local adjuvant treatment may be essential. While we have proved the value of prophylactic radiation therapy after radical esophagectomy for esophageal carcinoma with positive lymph node metastases and stage Ⅲ disease, there is still lack of clear evidence for postoperative radiation therapy in stage T2-3N0M0 disease now. The comparison of conventional two-dimensional radiotherapy after operation versus surgery alone does not show statistically significant difference for stage T2-3N0M0 disease in our previous report. In the precise radiotherapy setting, increasing evidence of non-randomized control studies indicated the trend or preliminary results of dosimetric advantages of IMRT translating into substantive benefits in both survival and local-regional control compared with three-dimensional conformal and two-dimensional conventional radiotherapy for the treatment of esophageal carcinoma, but it remains to be confirmed in the randomized controlled study that whether IMRT is effective to

improve clinical outcomes of stage T2-3N0M0 patients of TESCC. In view of this, we designed the randomized controlled trial to determine the clinical efficacy and safety of prophylactic IMRT after surgery in stage T2-3N0M0 disease of TESCC.

Study design

This is a prospective open-label, randomized, controlled clinical trial evaluating treatment efficacy and safety of postoperative radiotherapy in pathologic T2-3N0M0 thoracic esophageal squamous cell carcinoma patients without neoadjuvant therapy. Patients who received radical esophagectomy will be clearly examined by diagnostic imaging and underwent pathologic review. Eligible patients will be randomized to radiation or under observation (surgery alone). During follow-up, salvage chemotherapy or radiotherapy could be applied if there are recurrent or metastatic diseases. Determination of salvage regimen will be discussed on multidisciplinary panel.

Study schema



Patient eligibility

Inclusion criteria

1. Stage T2-3N0M0 disease of TESCC patients who received R0 resection and confirmed by pathological reviews;
2. Age 18 to 72 years;
3. KPS$\geqslant$70;
4. Did not receive neoadjuvant or adjuvant treatment;
5. No clear recurrent or metastatic lesions;
6. Intensity-modulated radiation therapy(IMRT) is accepted;
7. Adequate organ function;
8. Regular follow-up could be possible.

Exclusion criteria

1. Exploratory thoracotomy or palliative surgery;
2. Severe postoperative complications or comorbidities;

3. Recurrence or metastasis is not certain;
4. Secondary malignancies before treatment;
5. Irregular follow-up.

Radiotherapy

Radiation simulation

All patients were required fasting for at least 3 hours before simulation. Patients were immobilized in supine position with a thermoplastic mask covering neck, chest and upper abdomen. Contrast-enhanced CT scan including bilateral necks, supraclavicular area, chest and upper abdomen with 3mm slices were applied.

Target volumes

Target volumes were defined according to International Commission on Radiation Units and Measurements (ICRU) reports 83. Clinical target volume (CTV) was defined from cricothyroid membrane to 3cm below carina for proximal diseases, and from T1 vertebra to 3cm below tumor bed for middle and lower disease, which involved 1R/L, 2R/L, 3p, 4R/L, 7, part 8 and part10L mediastinal lymph nodes. Anastomosis was included when proximal tumor margin less than 3cm or for proximal disease. Planning target volume (PTV) included CTV and additional 5mm in three-dimensional directions. PTV was separated from upper edge of the clavicular head as PTV-upper and PTV-lower, the prescription doses were 50.4Gy for PTV-upper and 56 for PTV-lower in 28 fractions, five fractions per week. Normal tissue dose constraints are listed in Table P1. All plans were generated by medical physicists and reviewed by physicians. Step and shoot IMRT or volumetric modulated arc therapy (VAMT) technique were used. High dose points were especially avoided for residual stomach against possible mucosa erosion or bleeding. The trade-off between target volume coverage and normal tissue protection were finally determined by responsible physicians.

Statistical analysis

Sample size

Assuming a disease-free survival event rate of approximately 10% based on our experience and a relative risk reduction of 21.5% (5-year disease-free survival increase from 50.3% to 71.7%), a power of 80% and a two-tailed 5% type I error with six years of recruitment and five-year follow-up, the required sample size was determined to be 216 with 105 events. The study assumes 10% dropout or loss of follow-up, therefore we need 240 patients and 120 patients in each group. One interim analysis will be performed to allow for early termination of the trial in light of evidence that the postoperative radiotherapy is superior to the postoperative alone or there is no difference between the two treatment groups. In order to provide an overall significance level of 0.05 for the study, the interim analysis will use a Lan-DeMets monitoring boundary with an O'Brien-Fleming stopping rule. The interim analysis will be conducted when 50 events out of 105 events have been observed. Using O'Brien and Fleming's test boundaries, the Z-score test cut-off at the interim analysis for stopping and rejecting the null hypothesis will be 2.540, the Z-score test cut-off at the interim analysis for stopping and rejecting the alternative is 0.340 (Figure P1A, Figure P1B).

Statistical Analysis Plan

Descriptive statistics will be provided to summarize the patients' characteristics and toxicities by the treatment methods (postoperative radiotherapy and surgery alone). Chi-square test or Fisher's

exact test will be applied to compare the baseline characteristics of patients between two groups. The balance of the potential confounders between the two groups will be evaluated as well.
The main analysis will be performed based on the intention-to-treat principle (ie, including patients in groups to which they were randomized). Time-to-event outcomes (ie, primary outcome, disease-free survival; and secondary outcome, overall survival) will be presented using Kaplan-Meier survival curves. The treatment effect of postoperative radiotherapy group and the postoperative group will be evaluated using Cox proportional hazard regression model and expressed by hazard ratios (HRs) and 95% confidence intervals (CIs). Proportional hazard assumptions will be checked by visual inspection and a weighted residuals test and all criteria will be met. We will not use any method of data imputation. We will perform subgroup analyses according to the status of local-regional recurrence and distant metastasis using Kaplan-Meier Estimate, and the cumulative incidence can be obtained using 1 - KM survival rate.
All analyses will consider a two-tailed 5% type I error as the significance level for determining statistical significance difference and will be performed using R software (R Foundation for Statistical Computing).

Table P1. Normal tissue dose constraints

Organs at Risk	Dose constraints
Lungs	Dmean<16Gy, V20<28%, V5<65%
Heart	V30<40%, V40<30%
Cord PRV	Dmax<45Gy
Stomach	V40<50%, Dmax<55Gy
Liver	V30<30%
Kidneys	V20<40%

PRV = planning organ at risk volume
Dmean = mean dose to the target volume
Dmax = maximum point does to the target volume
V20 = percent of target volume received at least 20Gy dose
V5 = percent of target volume received at least 5Gy dose
V30 = percent of target volume received at least 30Gy dose
V40 = percent of target volume received at least 40Gy dose

Figure P1A. Critical constant under two-sided group sequential tests with K = 2 groups using O'Brien and Fleming's design

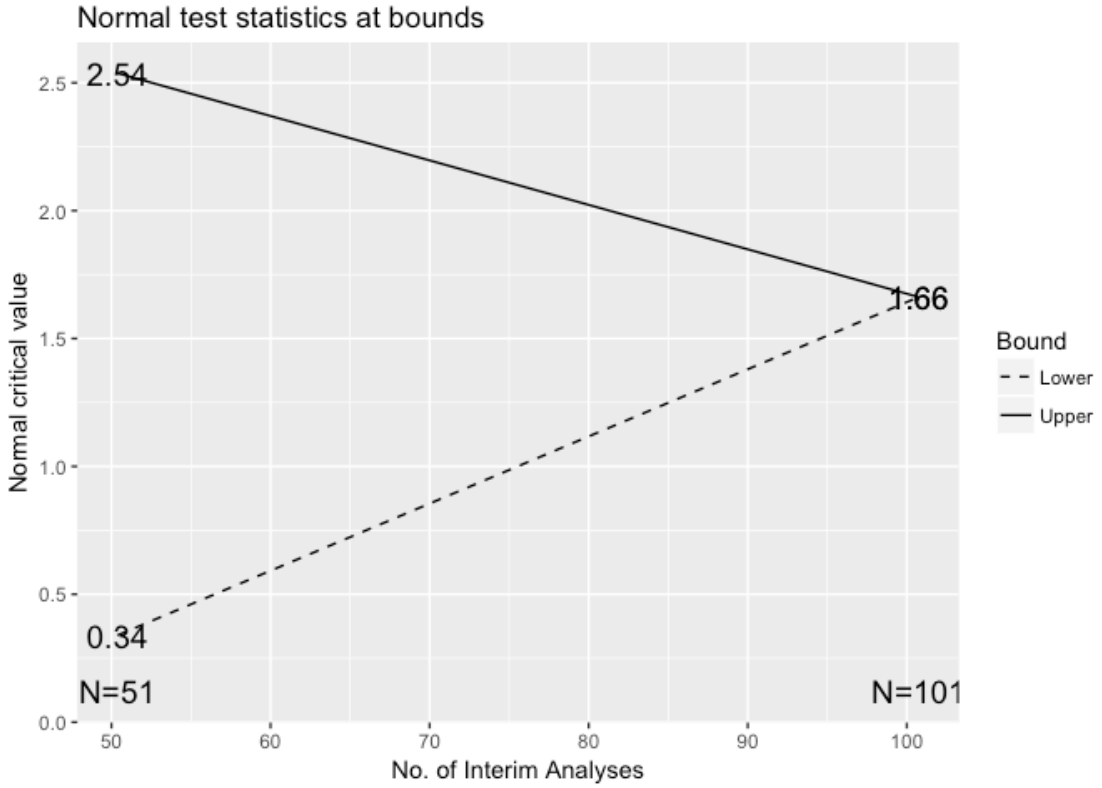


Figure P1B. Hazard ratio under two-sided group sequential tests with K = 2 groups using O'Brien and Fleming's design