Salvage photodynamic therapy for local failure after chemoradiotherapy for esophageal squamous cell carcinoma

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Background and Aims: Photodynamic therapy (PDT) is a less-invasive salvage treatment option for local failure at the primary site after chemoradiotherapy (CRT) for esophageal squamous cell carcinoma. The objective of this study was to clarify the long-term outcomes and prognostic factors of salvage PDT.

Methods: One hundred thirteen consecutive patients treated in our institution with PDT for local failure limited to within T2 without any metastases after definitive CRT performed between 1998 and 2008 were retrospectively enrolled. The complete response rate, adverse events, and survival outcomes were assessed and prognostic factors were investigated using a multivariate analysis.

Results: The complete response rate was 58.4% (95% confidence interval [CI], 49.3%-67.5%). The progression-free survival (PFS) and the overall survival (OS) rates at 5 years after salvage PDT were 22.1% (95% CI, 14.3%-30.0%) and 35.9% (95% CI, 26.7%-45.1%). N0 before CRT was significantly associated with OS (hazard ratio [HR], 0.54; 95% CI, 0.33-0.91, $P = .020$), whereas the impact of T1 or T2 before CRT on PFS (HR, 0.63; 95% CI, 0.38-1.04, $P = .068$) and that of a longer period between CRT and PDT on OS (HR, 0.64; 95% CI, 0.39-1.05, $P = .078$) were marginal. The treatment-related death rate was 1.8%.

Conclusions: Salvage PDT was found to have a superior outcome and a satisfactory safety profile. An earlier clinical stage before CRT and a longer interval between CRT and PDT may be associated with a longer survival period. (Gastrointest Endosc 2016;83:1130-9.)

INTRODUCTION

Chemoradiotherapy (CRT) is a definitive treatment option for esophageal squamous cell carcinoma (ESCC), and the complete response rate after CRT ranges from 30% to 90%, depending on the tumor stage.[1-3] Despite these outstanding efficacies, local failure after CRT, such as residual or recurrent lesions, remains a major obstacle to achieving a complete cure. A salvage esophagectomy is often performed with curative intent in such cases, and patients with an earlier tumor stage may have a better survival outcome.[4,5] However, salvage esophagectomy is associated with a higher incidence of postoperative adverse events and a higher mortality compared not only with primary surgery without any preoperative treatments but also with planned surgery after neoadjuvant CRT.[4-7] In a retrospective study, patients who achieved a complete response after CRT were unlikely to experience a recurrence in locoregional lymph nodes.[8] Taking the importance of local control at the primary site and the possible adverse events

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; EPS, esophagus-preserved survival; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; OS, overall survival; PDT, photodynamic therapy; PFS, progression-free survival.

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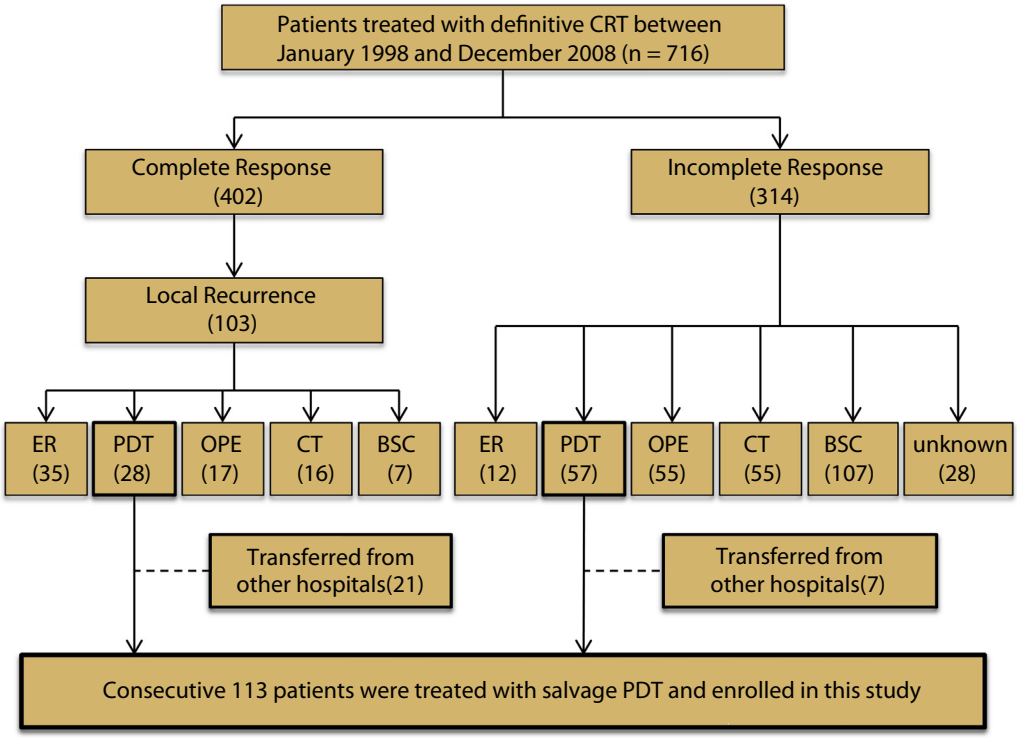

Figure 1. Treatment of patients throughout the study. *CRT*, chemoradiotherapy; *ER*, endoscopic resection; *PDT*, photodynamic therapy; *CT*, chemotherapy; *OPE*, operation; *BSC*, best supportive care.

of salvage surgery into consideration, we believe that endoscopic salvage treatment at the primary site could be a curative option in selected patients after CRT.

We have previously reported the acceptable efficacy and safety of salvage photodynamic therapy (PDT) for local failure after CRT for early stage ESCC in our institution as well as the favorable outcomes of a phase II study examining the treatment of lesions within T1 before PDT.[9,10] We have also previously reported some potential prognostic factors affecting survival outcomes. However, these prognostic factors might have some confounding biases with regard to their impact on survival outcomes. Because of the relatively small sample sizes and short follow-up periods of our previous studies, we could not evaluate the association of prognostic factors with possible confounding biases.

The aim of the present retrospective study was to clarify the long-term results and prognostic factors of salvage PDT for local failure after definitive CRT for ESCC by adjusting for confounding factors in a large cohort of patients with a long-term follow-up period.

METHODS

Patients

We retrospectively reviewed the data of all patients who underwent definitive CRT for ESCC between 1998 and 2008 at the National Cancer Center Hospital East, Kashiwa, Japan. Definitive CRT consisted of external beam irradiation of 50 Gy or more and concurrent chemotherapy with a fluoropyrimidine derivative with or without a platinating agent.

Patients who met the following criteria and had received PDT were retrospectively enrolled in this study: (1) absence of any lymph node or distant metastasis as observed using CT before PDT; (2) a residual or recurrent tumor at the primary site limited to within T2 as evaluated using EUS; (3) no indication for EMR because of ulceration or fibrosis caused by radiation or invasion of the deep submucosal layer; (4) patient's refusal to undergo salvage surgery or the presence of physical adverse events that would have made surgery intolerable; and (5) the provision of written informed consent.

Of the 716 patients treated with definitive CRT, 28 patients with a local recurrence and 57 with an incomplete response to CRT were candidates for PDT. Twenty-eight patients who had completed definitive CRT at other hospitals were referred to our institution for PDT (Fig. 1). All patient information was collected from medical records, including endoscopic images, radiologic images, and pathology reports. The study protocol was approved by the institutional review board in March 2011. The study was performed according to the ethical principles of the Declaration of Helsinki.

Evaluation of baseline clinical stage and effect of CRT

Clinical staging before CRT was determined based on the results of endoscopy, EUS, and contrast-enhanced CT