Clinical Oncology xxx (2018) 1–8

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Patterns of Failure Following Dose-escalated Chemoradiotherapy for Fluorodeoxyglucose Positron Emission Tomography Staged Squamous Cell Carcinoma of the Oesophagus

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Received 25 April 2018; received in revised form 5 June 2018; accepted 10 June 2018

Abstract

Aims: To analyse outcomes and patterns of failure following dose-escalated definitive chemoradiotherapy (CRT) for oesophageal squamous cell carcinoma using fluorodeoxyglucose positron emission tomography for staging and treatment planning.
Materials and methods: A retrospective review of patients with oesophageal squamous cell carcinoma receiving definitive CRT to a dose of ≥56 Gy was conducted. Patient and tumour characteristics, treatment received and first sites of relapse were analysed.
Results: Between 2003 and 2014, 72 patients were treated with CRT to a median dose of 60 Gy (range 56–66 Gy). The median age was 63 years; most (61%) were stage III/IVa. The median follow-up was 57 months. Three year in-field control, relapse-free survival and overall survival was 64% (95% confidence interval 50–75%), 38% (95% confidence interval 27–50%) and 42% (95% confidence interval 30–53%), respectively. Of the 41 failures prior to death or at last follow-up date, isolated locoregional relapse occurred in 16 patients (22%) with isolated in-field recurrence in 11 patients (15%). Distant failure as first site of relapse was present in 25 patients (35%). No in-field failures occurred in the 11 patients with cT1-2, N0-1 tumours. The median survival for cT4 tumours was 8 months, with five of eight patients developing local progression within the first 6 months.
Conclusions: Dose-escalated radiotherapy was associated with promising rates of in-field local control, with the exception of cT4 tumours. Distant failure remains a significant competing risk. Our data supports the need for current trials re-examining the role of dose escalation in the modern era.

Key words: Dose escalation; oesophageal cancer; radiotherapy; relapse; squamous cell carcinoma

Introduction

Combined modality therapy is standard of care for oesophageal squamous cell carcinoma (OSCC). Preoperative chemoradiotherapy (CRT) followed by surgery has shown improved survival over surgery alone [1], while definitive CRT offers an alternative treatment to surgery in locally advanced disease or patients not suitable for surgery due to comorbidities [2–4]. Following definitive CRT, local failure rates in the order of 50% have been reported [5–7]. Intensification of local therapy via escalation of radiation dose [8] or the addition of surgery to CRT [2,3] may improve local control, but these approaches have not been shown to significantly improve survival in previous randomised studies. The potential benefit may, however, have been diluted by competing risks such as under-staging, the use of older radiotherapy techniques and associated high treatment-related mortality. In the modern era, computed tomography (CT) planned three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) allow accurate delineation of tumour and

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https://doi.org/10.1016/j.clon.2018.06.011
0936-6555/

organs at risk with the potential for dose escalation with reduced toxicity. Furthermore, incorporation of fluorodeoxyglucose positron emission tomography (FDG-PET) has improved the accuracy of initial staging and further aids target delineation for radiotherapy [9–11]. Against this backdrop a new generation of randomised trials has recently been launched to test whether dose escalation in the modern era can deliver improved outcomes. Since 2003 our institution has used FDG-PET for staging and radiotherapy planning and treated OSCC with 3DCRT and concurrent chemotherapy to doses in the order of 60 Gy. The purpose of this retrospective study was to describe patterns of failure in this cohort and determine if this supports the investigation of radiation dose escalation in prospective randomised trials.

Materials and Methods

Patient Inclusion

Patients with biopsy-proven OSCC diagnosed between January 2003 and May 2014 were identified from a prospectively maintained database of all patients with carcinoma of the oesophagus presented through our multidisciplinary tumour meeting. The hospital ethics committee approved the collection and reporting of information in the database. All patients who were staged with FDG-PET and received definitive CRT to a dose of 56 Gy or higher were included for analysis. Over the study period, 238 patients with OSCC were treated with curative intent. Ninety-two patients were treated with a surgical approach (30 direct to surgery, 62 preoperative CRT) and 16 early stage lesions with endoscopic therapies. One hundred and thirty patients were treated with definitive CRT. Of these, 25 did not have initial FDG-PET staging recorded (most treated before FDG-PET was freely available), three patients received radiotherapy alone and 30 patients received <56 Gy, leaving 72 patients for the current analysis. We searched medical and radiotherapy records to collect outcome information, including site of relapse and salvage therapies.

Treatment

All cases were presented at a combined multidisciplinary upper gastrointestinal tumour meeting. Pre-treatment investigations included endoscopy, biopsy, CT of the neck, chest and abdomen and FDG-PET scan. Endoscopic ultrasound (EUS) was used selectively. Radiotherapy was delivered using 6–10 MV photons with a standard prescription of 60 Gy in 30 fractions over 6 weeks. Patients with lower third tumours were instructed to be nil by mouth for 3 h before planning and treatment. The gross tumour volumes (GTV primary and GTV nodal) included gross disease based on all clinical information (endoscopy, EUS, CT and PET findings). Rigid registration of PET-CT scans to the planning CT was carried out for patients treated from 2005. The clinical target volume (CTV) was the GTV primary plus a 0.5 cm radial margin and 3 cm craniocaudal margin along the oesophagus and GTV nodal plus a 0.5–1 cm isotropic margin. Elective nodal radiation was not undertaken for middle and lower third tumours. The upper mediastinal and supraclavicular fossa elective nodal groups were routinely included for cervical oesophageal tumours and variably included for upper third tumours. The planning target volume (PTV) was a minimum of CTV plus 1 cm. If required to reduce lung dose, a two phase technique was used, typically with a 10 Gy boost delivered to a reduced volume (1 cm craniocaudal CTV expansion on GTV). The protocol for target verification imaging changed over the study time period, with a weekly portal imaging protocol (daily during the first week) until 2010, daily kV imaging from 2010 to 2012 and daily cone-beam CT from 2013. Concurrent chemotherapy most commonly consisted of two cycles of cisplatin (80 mg/m^2) and a continuous 4 day infusion of fluorouracil (800 mg/m^2/day) during weeks 1 and 5 of the radiation course. Patients treated with carboplatin/paclitaxel received weekly administration of intravenous carboplatin (AUC 2 mg*min/ml) and paclitaxel (50 mg/m^2). Patients were not excluded from analysis if a different chemotherapy regimen was used.

Follow-up

Patients were typically followed-up 3 monthly for 2 years then 6–12 monthly with routine surveillance endoscopy. For patients who were clearly not candidates for salvage surgery, surveillance endoscopy was not mandatory after initial response assessment. Surveillance imaging was not routinely carried out until the latter half of the study, when a restaging FDG-PET/CT was generally obtained at 12 weeks post-treatment.

Recurrence

Locoregional failure was defined as persistent or relapsed tumour at the primary site and/or regional lymph nodes. Distant failure included non-regional nodal relapse and distant metastases. Radiotherapy plans were reviewed to further classify locoregional failures as in-field (within treated PTV) or out-of-field. Primary site failure required biopsy confirmation, whereas failure at other sites was based on clinical or radiological evidence. Failure occurred on diagnosis of relapse.

Statistical Analysis

The Kaplan–Meier product-limit method was used for survival analyses. Survival rates and associated 95% confidence intervals were calculated for overall survival, relapse-free survival, locoregional failure-free survival and distant metastasis-free survival. Time-to-event end points were calculated from the date of diagnosis to the date of the event. Hazard ratios from univariate and multivariate Cox regression analyses were obtained for predictors of locoregional failure, distant failure and overall survival. Patient, tumour and treatment factors included in models were age, gender, smoking status (never versus current/

Please cite this article in press as: Effeney R, et al., Patterns of Failure Following Dose-escalated Chemoradiotherapy for Fluorodeoxyglucose Positron Emission Tomography Staged Squamous Cell Carcinoma of the Oesophagus, Clinical Oncology (2018), https://doi.org/10.1016/j.clon.2018.06.011