Clinical Oncology xxx (2017) 1–6

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Ninety Day Mortality After Radical Radiotherapy for Head and Neck Cancer

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Received 20 June 2017; received in revised form 31 July 2017; accepted 2 August 2017

Abstract

Aims: Treatment for head and neck cancers using definitive radiotherapy, with or without chemotherapy, is associated with significant acute toxicity. Our aim was to assess 90 day mortality after radical radiotherapy. A further aim was to identify patient, tumour or treatment factors associated with early death after treatment and whether these could be used to predict outcomes.

Materials and methods: In total, 1116 patients with squamous cell pharyngeal and larynx cancer between January 2011 and December 2015 were included. Patients with T1 larynx cancer were excluded. Patients were treated using radical radiotherapy, with or without chemotherapy. Ninety day mortality was calculated using survival of less than 135 days from the planned start date for radical radiotherapy, to include early deaths during and up to 90 days after treatment.

Results: Overall, 90 day mortality was 4.7%. Among the subgroup of patients treated with concurrent platinum chemotherapy, the 90 day mortality rate was 0.4%. Overall survival at 1, 3 and 5 years was 84%, 62% and 53%, respectively. Factors associated with a higher risk of early death included performance status >1, haemoglobin <100 g/l, weight <60 kg, age >80 years and presence of multiple comorbidities.

Conclusion: We report excellent crude overall survival rates among our radically treated cohort of head and neck cancer patients. Several factors were associated with an increased risk of death within 90 days of completion of radical head and neck radiotherapy. Given the potential severe acute effects and the impact on patient quality of life associated with radical head and neck radiotherapy, this information is helpful to inform treatment-related discussions with patients.

Key words: 90 day mortality; head and neck; intensity-modulated radiation therapy; radical radiotherapy; squamous cell cancer

Introduction

The incidence of head and neck cancer in the UK is about 8000 per year and it accounts for 2700 deaths per year [1]. Radical radiotherapy, with or without synchronous chemotherapy, is associated with significant treatment-related toxicity. Ninety day mortality after the completion of radical radiotherapy is a proposed measure for improving cancer outcomes and to reduce avoidable treatment-related harm [2]. The Scottish Cancer Taskforce recommended that 90 day mortality after curative treatment for head and neck cancer was used as an indicator for quality of care, ensuring curative treatments are undertaken appropriately [3].

The DAHNO Audit (2014) showed 3.6% 90 day mortality in patients treated with radiotherapy for head and neck cancer [4]. Studies of unselective disease sites have shown 90 day mortality rates of 1.7% and 4.8% after radical radiotherapy [5,6]. There are few published reports of 90 day mortality specific to head and neck carcinoma, although there are reported rates of early mortality after radical chemoradiotherapy of between 5.4 and 18% [7–9]. It has been suggested that a target for 90 day mortality should be $<5\%$ for all radical treatments, across all disease groups [10].

The primary aim of this project was to assess 90 day mortality after the completion of radical radiotherapy for head and neck cancer. The secondary aims were to identify patient, tumour or treatment factors that are associated with early death after treatment and whether these could

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http://dx.doi.org/10.1016/j.clon.2017.08.005
0936-6555/

be used to predict outcomes. Given the severe acute effects and impact on patient quality of life associated with radical head and neck radiotherapy, this information is important to help inform discussions about treatment with patients.

Materials and Methods

Patient Details

This study included all patients with squamous cell pharyngeal, laryngeal and oral cavity head and neck cancers (excluding T1 larynx cancer) where the treatment intention was to deliver definitive radiotherapy at The Christie NHS Foundation Trust between January 2011 and December 2015. Patients were excluded if they received postoperative radiotherapy after surgery to the primary disease site. In total, 1116 patients were identified; demographics, clinical information and treatment details were collected from electronic patient records. Performance status was graded using World Health Organization criteria. The Adult Comorbidity Evaluation Index (ACE27) score was used as an indicator of comorbidities, with a scale of 0–3, where 0 indicates no comorbidities and 3 indicates significant comorbidities. TNM staging was obtained from notes and overall group staging calculated depending on the site of primary tumour.

Treatment Details

Radiotherapy was delivered using conformal or intensity-modulated radiation therapy, depending on the tumour site and stage. Volumetric-modulated arc therapy was used from 2013 onwards. The standard therapeutic radiotherapy doses were: 66 Gy in 30 once-daily fractions of 2.2 Gy over 6 weeks, 55 Gy in 20 once-daily fractions of 2.75 Gy over 4 weeks and, for nasopharynx cancer, 70 Gy in 33 once-daily fractions of 2.12 Gy over 6.5 weeks. Systemic therapy was used for fit patients with locally advanced disease. The standard induction chemotherapy regimen was docetaxel, cisplatin and 5-fluorouracil; concurrent chemotherapy was single-agent cisplatin. Synchronous carboplatin or cetuximab were substituted in patients who were not suitable for cisplatin. All patients were reviewed weekly by medical teams during treatment and 6 weekly during the initial follow-up. Patients were referred to speech and language therapy and dietetics before treatment and input during radiotherapy weekly review clinics.

Statistical Analysis

The maximum number of planned fractions for radical head and neck treatment was 33, with a maximum planned overall treatment time of 45 days. Survival was calculated from the planned start date for radical radiotherapy, including any patient who survived less than 135 days after the start of radiotherapy, as a surrogate for 90 day mortality post-radical radiotherapy. Patient outcomes were based on intention-to-treat analysis. The statistical analysis was carried out using R and Graph Pad Prism version 7. The chi-squared test was used to assess differences between the two subgroups analysed across a series of variables. Logistic regression was used to assess the association between exploratory variables and outcome one at a time. Variables included: age, performance status, ACE27 comorbidity score, pretreatment weight, primary disease site, disease stage, smoking status, alcohol intake, pretreatment haemoglobin and previous neck dissection. The likelihood ratio test was applied to assess the significance of the association. Significance was assessed at the $P < 0.05$ level. Multivariate analysis incorporated the most significant variables from the univariate analysis stage and was applied to assess the association between variables and outcome taking into account other variables in the model at the same time. Profile likelihood confidence intervals and corresponding P values were calculated for odds ratios both at univariate and multivariate analysis.

Results

In total, 1116 patients who received radical head and neck radiotherapy, 53 (4.7%) died during or within 90 days from the completion of treatment. The 1 year overall survival rate was 84%, whereas the 3 and 5 year overall survival rates were 62% and 53%, respectively. Patient demographics and treatment factors are described in Table 1, with staging information in Table 2. There were significant differences between those who died within 90 days and those who survived in patient age, performance status, ACE27 comorbidity score, weight, chemotherapy use and haemoglobin level.

Certain subgroups had better outcomes, in particular those patients treated with concurrent platinum chemotherapy had a 90 day mortality rate of 0.4% (2/459). Those treated with induction chemotherapy had 0% 90 day mortality (0/204). Patients $\leq$ 70 years had 3.5% 90 day mortality compared with 8.9% in those aged over 70 years. Those with a performance status 0/1 or ACE27 0/1 also had reduced 90 day mortality of 2.6% (25/950) and 3.5% (28/799), respectively.

Of those who died during or within 90 days of treatment, the median age was 69 years (range 47–89 years). Two were initially planned for radical treatment, but changed to a high dose palliative regimen before starting treatment. Eleven patients (21%) only received 10 or fewer fractions and two (4%) did not receive any treatment.

On univariate analysis, the variables most significantly associated with a likelihood of death within 90 days of treatment completion were: age, performance status, ACE27 comorbidity, weight and haemoglobin level. Increasing performance status and ACE27 score were associated with an increased likelihood of early mortality, together with lower weight and haemoglobin levels. Older patients also had an increased risk of dying within 90 days, particularly those over 80 years old. Smoking status, alcohol intake and overall tumour stage showed no association. Odds ratios are displayed in Table 3 and Figure 1. On

Please cite this article in press as: Dixon L, et al., Ninety Day Mortality After Radical Radiotherapy for Head and Neck Cancer, Clinical Oncology (2017), http://dx.doi.org/10.1016/j.clon.2017.08.005