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Fatigue during chemoradiotherapy for nasopharyngeal cancer and its relationship to radiation dose distribution in the brain

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ABSTRACT

Background and purpose: Fatigue during head and neck radiotherapy may be related to radiation dose to the central nervous system (CNS). The impact of patient, tumour, and dosimetric variables on acute fatigue was assessed in nasopharyngeal cancer patients undergoing chemoradiotherapy.

Material and methods: Radiation dose to the following retrospectively-delineated CNS structures; brainstem, cerebellum, pituitary gland, pineal gland, hypothalamus, hippocampus and basal ganglia (BG) and clinical variables were related to incidence of $\geqslant$ grade 2 fatigue in 40 patients.

Results: Sixty per cent of patients reported fatigue during and following radiotherapy. Dmean and D2 to the BG and Dmean to the pituitary gland were significantly associated with fatigue during radiation ($P < 0.01$). Dmean to the cerebellum was associated with fatigue following radiotherapy and at any time ($P < 0.01$). After adjusting for clinical factors, an association remained between fatigue during radiotherapy and mean dose and D2 to the pituitary gland and BG ($P = 0.012$, 0.036, 0.009 and 0.018) and mean dose to the cerebellum following radiation and at any time ($P = 0.042$ and 0.029).

Conclusion: Disruption of connections between BG, cerebellum, and higher cortical centres or disruption of pituitary-regulated hormonal balance may be implicated in the pathophysiology of radiation-related fatigue.

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Fatigue is one of the most common and distressing symptoms reported during head and neck radiotherapy (RT), occurring in more than 50% of patients [1–5], but remains poorly understood. It has been recognised as a major cause of psychological disturbance, distress and reductions in functional status and quality of life [6–8]. Head and neck cancer (HNC) patients who undergo definitive chemo-radiotherapy (CRT) experience substantial acute side effects including severe dysphagia, mucositis, exudative dermatitis, xerostomia, and hypogeusia/ageusia [9]. Amongst these problems, fatigue is often underestimated, and even ignored by the clinician [10]. As a consequence, radiation-induced fatigue has been poorly studied. However, it can negatively affect patients' compliance with treatment and, therefore, a better understanding of this condition is sought.

The reason why some patients develop significant fatigue during RT is not known. It has been suggested that fatigue may be related to the type of cancer [11], the pre-treatment level of fatigue [1,2,12], or the duration of the radiation treatment course [13–15]. Some other factors such as decline in neuromuscular efficiency [16], weight loss, decreasing haemoglobin levels during treatment [17], pain [18,19], or negative mood and stress caused by the daily confrontation with the disease have also been proposed. Studies have suggested an association between fatigue and circulating inflammatory cytokine levels [20]. More recently, we have reported that patients with oropharyngeal and hypopharyngeal carcinoma treated in the phase 3 randomised PARSPORT trial experienced significantly more acute fatigue when irradiated with intensity modulated radiotherapy (IMRT) as opposed to 3D conformal RT [21]. The subsequent dosimetric analysis showed that the excess fatigue reported in the IMRT arm of this trial may be attributable, at least in part, to increased dose to the posterior fossa, cerebellum and brainstem [22].

The aims of this current study were prospectively to analyse fatigue levels and their evolution during treatment in a consecutive series of patients undergoing IMRT for nasopharyngeal cancer (NPC) and to evaluate the impact of patient-, tumour-, and treatment-related variables on the grade of fatigue.

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Materials and methods

Patient characteristics

Patients with newly diagnosed histologically confirmed (T1–4, N0–3, M0) squamous cell or undifferentiated NPC (WHO Types I–III) were prospectively treated with primary chemoradiotherapy (CRT) in a phase II trial approved by local research and ethics committees (CCR 2608/, 05/Q0801/74). Disease was staged according to the 2002 American Joint Committee on Cancer criteria (AJCC) [23]. Acute fatigue was defined as a secondary endpoint. The primary endpoint was the proportion of patients suffering xerostomia of grade 2 or more, assessed using both the RTOG and LENT/SOMA late toxicity scores, one year after treatment.

Treatment characteristics

Systemic treatment

Thirty-eight patients received induction chemotherapy: two cycles of cisplatin (CDDP, 75 mg/m^2, day 1) and 5-fluorouracil (5-FU, 1000 mg/m^2, days 1–4) on a 21-day cycle. In addition to CDDP-5-FU, docetaxel 75 mg/m^2 was administered in 2 patients. Patients received concomitant cisplatin 100 mg/m^2 on days 1 and 29 of IMRT. In patients for whom cisplatin was contraindicated because of hearing loss or kidney dysfunction, carboplatin (AUC = 5) was substituted. One patient unsuitable for chemotherapy received concomitant cetuximab (400 mg/m^2 loading dose and 250 mg/m^2 weekly).

During treatment, haemoglobin (Hb) was measured regularly and anaemia was defined as Hb <12 g/dL in both men and women. On the basis of previously published evidence [24], patients receive blood transfusion to correct Hb concentrations <11.5 g/dL, to a target Hb concentration of >11.5 g/dL. Lowest Hb values during RT and up to 2 months after completion of treatment were recorded.

IMRT planning and delivery

Patients were immobilised during computed tomography (CT) acquisition and treatment using a 5-point custom-made thermoplastic mask [25]. Contrast-enhanced CT scans with a slice thickness of 2–5 mm were obtained from the vertex of the scalp to 5 cm below the clavicular heads. Clinical target volume (CTV) included the nasopharynx, bilateral parapharyngeal spaces, the posterior half of the nasal cavity, inferior half of sphenoid sinus (or entire sphenoid if involved), retropharyngeal nodes and involved nodal levels with a 3 mm margin to construct the planning target volume (PTV1). The nodal levels at risk of microscopic disease and the superior half of the sphenoid sinus were incorporated into a second volume (PTV2). Elective nodal irradiation volumes were outlined as in the consensus guidelines [26].

IMRT was delivered using dynamic multileaf collimation, using five or seven beams and a simultaneous integrated boost technique, delivering 65 Gy in 30 daily fractions to PTV1 and 54 Gy in 30 daily fractions to PTV2. Critical structures included parotid glands, submandibular glands, spinal cord, brainstem, mandible, oral cavity, optic chiasm and optic nerves. The maximum dose constraints applied to the optic chiasm, optic nerves, brainstem and spinal cord were 54, 55, 54, and 48 Gy, respectively. Mean parotid dose was set at 26 Gy.

Data collection

Toxicity assessment

Acute fatigue score was recorded at baseline, (prior to radiotherapy), weekly during CRT, and at weeks 1–4 and 8 following completion of RT. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 2.0 was used; grade 1 (G1) referring to increased fatigue but no change in normal activities, grade 2 (G2) to moderate fatigue or causing difficulty in performing some activities of daily living (ADL), and grade 3 (G3) to severe fatigue interfering with ADL.

CNS structure delineation

Potential intra-cranial fatigue at-risk structures (FARS) that were analysed included brainstem, cerebellum, pituitary gland, pineal gland, hypothalamus, combined left and right hippocampus and combined left and right basal ganglia. Following an institutional outlining protocol (Supplementary Appendix 1 and Fig. 2), these structures were delineated by two experienced head and neck radiation oncologists (CP and US). For 5 randomly selected patients, the FARS were independently delineated by both radiation oncologists to assure that they conformed to the institutional protocol. FARS were delineated on the original planning CT, within Eclipse ($N = 33$) or Pinnacle ($N = 7$) treatment planning software, as two different softwares are used across the two sites of our institution.

Data analysis

The maximum grade of acute fatigue was considered for three time periods, as follows: during RT (weeks 1–6); following RT (weeks 1–4 and week 8); and the combination of these two time periods.

The clinical variables examined for correlation with acute fatigue included age, gender, T stage (T1/2 versus T3/4), N stage (N0/1 versus N2/3), lowest haemoglobin value and type of induction and concomitant CT, respectively. In addition to these clinical variables, dose distributions to each brain structure, using the mean (Dmean) and the near maximum dose (dose to 2% of the volume, D2) as per the ICRU 83 recommendations [27] were analysed. Absolute doses are reported without adjustment to EQD2.

Dose to FARS was assessed for normality using the Shapiro–Wilk test and found to be sufficiently normally distributed ($P > 0.05$) for the use of parametric testing, with the exception of dose to the pituitary and pineal glands for which non-parametric equivalents were used. Independent t-tests (or non-parametric Mann–Whitney tests) were used to compare these dosimetry data (Dmean and D2) for each structure between the group of patients who reported $\geqslant$G2 fatigue and the group of patients who did not. This analysis was performed for each of the time periods considered. Logistic regression was used to investigate the odds of developing fatigue during RT depending on doses to FARS and clinical characteristics. Doses to FARS which differed significantly between the 2 groups on univariate analysis were entered into multivariable regression models with all clinical variables (regardless of statistical significance). A level of $P < 0.01$ on two-tailed tests was considered significant to make some allowance for multiple testing. All statistical calculations were carried out using the statistical package Stata v11 (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP).

Results

Between March 2006 and January 2010, 40 patients were recruited into this phase 2 study. Patient and tumour characteristics are summarised in Table 1. The median fatigue scores recorded were 1 (range 1–3), 1 (range 0–3) and 2 (range 1–3) during radiotherapy (weeks 1–6), following radiotherapy (weeks 1–4 and 8) and the maximum fatigue score recorded at any time, respectively. The distribution of fatigue scores at each analysis time point is shown in Fig. 1 with 60% of patients experiencing $\geqslant$grade 2 fatigue during or after treatment.