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Hyperfractionated Compared with Conventional Radiotherapy in Oropharyngeal Carcinoma: an EORTC Randomized Trial

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INTRODUCTION

IN PURE hyperfractionation, radiotherapy is given in a higher number of fractions with a smaller dose per fraction, within the same overall treatment time as in conventional fractionation regimens (1). Division of the daily dose into two fractions (with an 8 h interval between them) allows for better recovery of normal tissues, which determines the late radiation tolerance. This gain in tolerance can be exploited by giving a 15% higher total dose in the same overall time. Whether such an increase in dose improves locoregional control without increasing the complication rate was the question addressed by trial 22791 of the EORTC Cooperative Group of Radiotherapy.

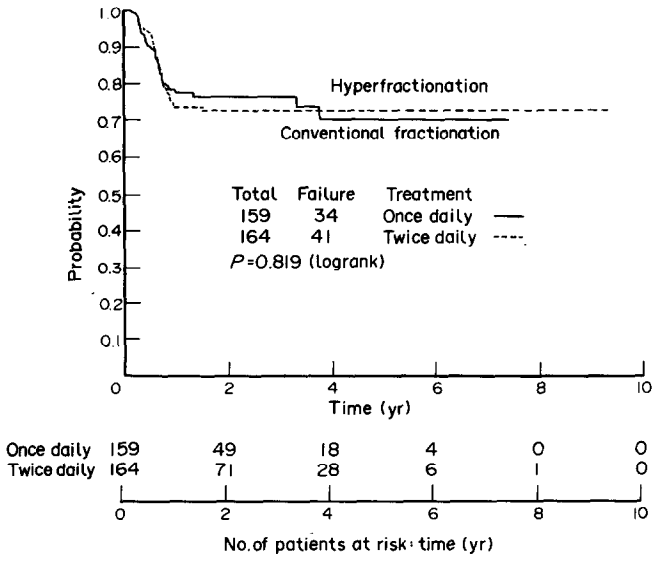

Fig.1. Probability of avoiding late side-effects of grade 2 or 3.

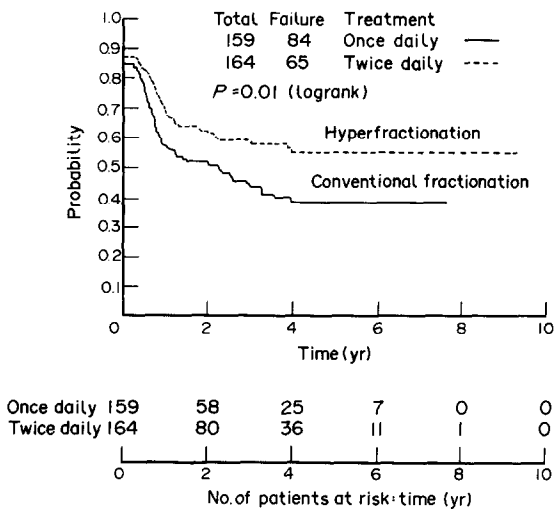

Fig.2. Probability of remaining free of locoregional disease.

PATIENTS AND METHODS

Patients had T2 T3 N0 or N1 oropharyngeal squamous cell carcinoma under 3 cm in size (except for primaries arising from the base of the tongue). Patients were randomly allocated to conventional fration ation (70 Gy in 35 fractions over 7 weeks) or hyperfractionation (80.5 Gy in 70 fractions over 7 weeks). From 1980 to 1987, 356 patients were entered by 28 institutions from seven European countries. 90% of the patients were evaluable for the final analysis.

Acute and late tolerance

Objective acute tolerance based upon the scoring of acute mucosal reactions (according to the EORTC scoring scales for acute and late radiation damage) was significantly decreased in the hyperfractionation arm ($P = 0.007$ logrank, chi square test for trend), resulting in a prolongation of the overall treatment time in 13% of the patients. Only 6% of cases did not reach the prescribed dose.

Late damage to normal tissues was evaluated with an actuarial estimate of the freedom from grades 2 and 3 late tissue damage (Fig. 1). No difference was observed between the two treatment arms, which confirms the accuracy of the radiobiology prediction for normal tissue tolerance in the head and neck area. These results are of particular interest for the slower proliferating normal tissues such as bone and connective tissues.

Locoregional control

The locoregional control was significantly higher ($P = 0.01$ logrank) after hyperfractionation compared with conventional fractionation (Fig. 2). At 5 years, 56% of patients are locoregional disease-free in the hyperfractionated arm, as compared to 38% in the conventional fractionation arm. This advantage was observed only in the 217 patients with a good initial performance status (Karnofsky index 90–100%). The superiority of hyperfractionation was also demonstrated in patients staged T3 N0 T3 N1 but not in T2. The Cox model confirmed that the treatment regimen was an independent significant prognostic factor for locoregional control ($P = 0.007$, logrank).

Survival

Survival was not an end-point in our study. However, the improvement of locoregional control was responsible for a trend to an improved survival ($P = 0.07$, logrank).

CONCLUSIONS

This is the first controlled trial of the benefit of delivering 2 fractions per day instead of 1. We stress the importance of selecting patients in good general condition and with moderately advanced tumours to assess improvements of radiotherapy regimens in head and neck carcinoma. These positive results strongly support clinical research of new schemes of radiotherapy designed after cooperation between radiobiologists and radiotherapists. The present trials (ref. 2 and EORTC protocol 22851) include comparisons of conventional fractionation and accelerated fractionation (same total dose within a shorter overall treatment time) with individual measurements of tumour kinetics. Future trials should try to demonstrate the respective indications for conventional fractionation, hyperfractionation and accelerated fractionation, based upon clinical presentation and cell kinetics.

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