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CLINICAL INVESTIGATION **Head and Neck**

WHY TO START THE CONCOMITANT BOOST IN ACCELERATED RADIOTHERAPY FOR ADVANCED LARYNGEAL CANCER IN WEEK 3

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Purpose: We analyzed toxicity and the local control rates for advanced laryngeal cancer, treated with two accelerated fractionation schedules. The main difference between the schedules was the onset of the concomitant boost, in Week 3 or Week 4. Overall treatment time and total dose were equivalent.

Methods and Materials: In a prospective, nonrandomized study of T_3, T_4, and advanced T_2 laryngeal cancer, concomitant boost schedules were used in 100 patients. Thirty patients received a schedule of twice daily 1.2 Gy in Weeks 1–3, followed by twice daily 1.7 Gy in Weeks 4 and 5; total dose was 70 Gy (the hyperfractionated accelerated schedule [HAS] regimen). Seventy patients were treated with 5 times 2 Gy in Weeks 1 and 2, followed by daily 1.8 Gy and 1.5 Gy (boost) in Weeks 3–5; total dose 69.5 Gy (the accelerated schedule only [ASO] regimen). Distribution of T stage was 47%, 40%, and 12% for T_2, T_3, and T_4, respectively. In 24% of the patients, lymph nodes were positive. Pretreatment tracheotomy or stridor or both occurred in 8 patients. The distribution of prognostic factors was not significantly different between the two fractionation schedules. Acute and late toxicity was assessed. Results were estimated by the use of actuarial methods. For late toxicity and local control univariate and multivariate analyses were performed. Tumor control probability analysis was used to model cure rate differences.

Results: Overall acute mucositis score was equal for both schedules. Acute mucositis started and decreased significantly earlier in the HAS regimen. In all patients acute mucositis healed completely. The treatment was completed within 38 days in all patients. The regional control rate was 100% for clinical N_0, and 75% for the clinical N_+ patients. The 3-year local control rate was 59% and 78% for the HAS and ASO regimens, respectively ($p = 0.05$); the ultimate local control was 80% and 94%, respectively. In multivariate analysis, besides the fractionation schedule (relative risk [RR], 2.6 for HAS vs. ASO), pretreatment tracheotomy/stridor (RR 4.3, yes vs. no), and local tumor response 3–6 weeks after radiotherapy (RR 5.1, no vs. yes) were independent factors for local control. Tumor control probability analysis indicated that the onset of repopulation may be about 4–6 days earlier for the HAS regimen. The onset of repopulation in the HAS regimen is probably at the end of the second week or at the beginning of the third week. Severe late toxicity was observed in the HAS group and ASO group in, respectively, 11% and 16%. In multivariate analysis this toxicity related significantly to the field size and pretreatment tracheotomy/stridor.

Conclusions: In our study the timing of the boost in accelerated radiotherapy for advanced laryngeal cancer was an independent factor for local control, favoring the use of a concomitant boost in Week 3. This finding may indicate that accelerated repopulation of tumor cells starts early in the treatment phase. © 2005 Elsevier Inc.

Laryngeal cancer, Accelerated fractionation, Repopulation, Local control, Toxicity.

INTRODUCTION

Primary radiotherapy of tumors of the larynx has the obvious advantage of preservation of the natural voice. With conventional radiotherapy for T_2 tumors local control may drop from 80% if the mobility of the vocal cord is normal, to 70% when the mobility is impaired (1). In T_3 laryngeal tumors a dose–response relationship has been shown (2), favoring a total dose of in excess of 66 Gy with an expected local control rate of 50–60%.

Improvement of local control for advanced T_2, T_3, and selected T_4 tumors may be reached by the use of altered fractionation schedules. The randomized Radiation Therapy Oncology Group trial (RTOG 9003) showed that accelerated fractionated radiotherapy significantly improved local control rate (54%) compared with conventional radiotherapy (43%), in patients with Stage III/IV supraglottic cancer (3). The accelerated fractionation schedule used a concomitant boost, starting in Week 5, delivering 72 Gy in 42 fractions over 6 weeks. The gain in overall treatment time

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compared with the conventional arm was 1 week. Further reduction of the overall treatment time may result in further improvement of local control. However, a treatment shorter than 5 weeks may lead to increased toxicity and may necessitate reducing the total dose (4).

In 1994 we started a first prospective study for patients with advanced laryngeal cancer, in which we reduced the overall treatment time to 5 weeks by the use of a concomitant boost schedule, starting in Week 4 with twice daily doses of 1.7 Gy. In the first 3 weeks we applied hyperfractionation, twice daily doses of 1.2 Gy. The timing of the start of the concomitant boost schedule was based on the presumption that accelerated repopulation of tumor cells in head and neck cancer begins in the fourth week of a conventional fractionation schedule (5). Our first study was the hyperfractionated accelerated schedule (HAS). In the HAS study, 50 fractions were used, which in clinical practice was felt as a burden for the patient and took up too much of the treatment capacity of the Department of Radiotherapy.

In a second prospective study, starting from 1997, the number of fractions was reduced to 40. The concomitant boost with doses of 1.5 Gy was started from Week 3, and no hyperfractionation was used in the first 2 weeks. This regimen will be indicated as the accelerated schedule only (ASO) regimen. Overall treatment time in the ASO study was 5 weeks. In the presumption of no, or only a short, delay of onset of accelerated tumor cell repopulation, the start of the concomitant boost in Week 3 compared with Week 4 should result in higher local control rates.

The aim of this study is to analyze acute and late toxicity, and locoregional control of both schedules, and to provide clues to the differences in locoregional control observed.

METHODS AND MATERIALS

In a prospective, nonrandomized study undertaken by the joint clinics of ENT and Radiotherapy of the University Medical Center Utrecht, 102 patients with previously untreated advanced laryngeal cancer ($n = 95$) or hypo/oropharyngeal cancer ($n = 7$) were irradiated. The toxicity and locoregional control was analyzed. Patients were entered into the study from October 1994 until August 2002. Exclusion criteria were World Health Organization performance status of 2 or more, extensive cartilage invasion or invasion of the skin, neck nodes with a size of more than 3 cm, M_1, and severe shortness of breath related to the tumor volume. Diagnostic workup included panendoscopy, computed tomography (CT) scanning of the head and neck, and ultrasonography of the neck with fine-needle cytology for suspected lymph nodes. Acute side effects were scored weekly during treatment and after therapy until recovery was shown. After treatment evaluations were performed once every 2 months during the first 2 years, every 3 months in the third year, every 4 months in the fourth year, and from then on, every 6 months.

Treatment

Two accelerated fractionation schedules were used, both with an overall treatment time of 5 weeks and a total dose of 70 Gy (HAS) and 69.5 Gy (ASO). Patients were treated 5 days a week. When treatments were given twice daily, an interval between fractions of at least 6 hours was used. The initial treatment volume included the primary tumor, metastatic neck nodes, and clinically uninvolved draining nodes. The boost dose was given to the primary tumor and positive neck nodes. The primary tumor and bilateral neck nodes were treated with 6 MV photon beams. In general, patients were treated by lateral opposed beams. For node-positive patients the supraclavicular nodes were treated with an anterior photon field.

The first schedule (HAS) started in 1994. During the first 3 weeks, daily 2×1.2 Gy was administered to the initial treatment volume. In Weeks 4 and 5, patients were treated with 2 fractions of 1.7 Gy daily. The first daily fraction of 1.7 Gy was delivered to the boost volume, and the second fraction of 1.7 Gy to the initial treatment volume. After 39.4 Gy the spinal cord was shielded, and the posterior positive neck nodes were treated with lateral electron beams. Subsequently, the total dose was 70 Gy to the primary tumor and positive neck nodes, and 53 Gy to the clinically uninvolved neck nodes. The second schedule (ASO) started in 1997. The hyperfractionation part was abandoned, and the accelerated part was moved forward to the third week. In the first 2 weeks the dose per fraction to the initial treatment volume was 2 Gy. In Weeks 3–5, patients were treated with a fraction dose of 1.5 Gy to the boost volume. A second daily fraction dose of 1.8 Gy was delivered to the initial treatment volume. After 47 Gy the spinal cord was shielded, and the posterior positive neck nodes were treated with lateral electron beams. Subsequently, the total dose was 69.5 Gy to the primary tumor and positive neck nodes, and 47 Gy to the clinically uninvolved neck nodes.

Two patients were excluded from the analysis, both designated to get the ASO schedule. The first patient refused 2 weeks after the start of radiotherapy the accelerated part of the treatment and was further treated conventionally. The second patient had to be excluded owing to a moderate general condition after a neck dissection, performed before the start of radiotherapy. Subsequently, 100 patients remained for analysis, 30 treated with HAS and 70 with ASO.

Patient characteristics

All patients received a minimum follow-up of 16 months, or until death. The mean follow-up was 42 months, and it was 53 months for patients alive at the last follow-up: for HAS 79 months and for ASO 45 months. No patient was lost to follow-up. For estimation of local control rates, actuarial survival was used.

The mean age was 61 years (range, 40–81 years). Eighty-three percent of the patients were male. Only 5% of the patients did not smoke lifelong at all. Thirteen percent continued their smoking habits during radiotherapy, and 13% relapsed into the same habit after radiotherapy.

All patients had squamous cell carcinoma, moderately differentiated in 82%.

The patients were staged according to the International Union Against Cancer (UICC) 1992 TNM classification. The distribution of advanced T_2, T_3, and T_4 was 47%, 40%, and 12%, respectively. Positive lymph nodes were diagnosed in 24% (11% N_1, 7% N_{2b}, 6% N_{2c}), and were equally distributed among T stages. In primary supraglottic tumors, significantly more positive nodes (38%) were seen compared with primary glottic tumors (11%, $p = 0.008$).

The origin of the tumor was in the glottic area in 47%, in the supraglottic region in 45% of the patients, in the subglottis in 1%, and in the hypo/oropharynx in 7%.

In 6 patients, progressive shortness of breath developed during the time elapsed between the first visit and the start of radiother-