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Original research article

Hypofractionated accelerated radiotherapy in T1–3 N0 cancer of the larynx: A prospective cohort study with historical controls

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ABSTRACT

Aim: The goal of this prospective study was to assess the effectiveness of a hypofractionated accelerated regime in treatment of the larynx cancer.

Background: Multiple radiotherapy delivery regimes are used for treatment of the larynx cancer. Hypofractionated regimes could provide similar results with reduced use of radiotherapy facilities.

Material and methods: 223 patients with squamous cell carcinoma of the upper or middle larynx have been treated with 63 Gy delivered in 28 fractions of 2.25 Gy during 38 days, 5 fractions per week. The study endpoints were overall survival, progression-free survival, early and late treatment toxicity. Standard and accelerated radiotherapy groups from the study published by Hliniak et al.[20] served as controls.

Results: Five-year actuarial overall survival was 87.5% in the study group, 84.5% in the control group receiving accelerated radiotherapy (33 fractions of 2.0 Gy, 6 fractions per week) and 86.2% in the control group (33 fractions of 2.0 Gy, 5 fractions per week). Five-year progression-free survival was 73.6%, 77.2% and 66.2%, respectively. Overall, treatment toxicity and complication rates did not differ between the study group and the control groups.

Conclusions: The hypofractionated accelerated radiotherapy protocol using 5 fractions per week reduced the use of radiotherapy facilities. There was no significant difference in overall survival and progression-free survival between the study and control groups treated with accelerated or standard radiotherapy.

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1. Background

Complex relationships between total radiation dose, radiotherapy (RT) duration, number of fractions, and dose per fraction have been frequently studied.[1–4] It has been estimated that longer RT duration reduces local control of the tumor by 3–25% (median 15%) after 1 week and 5–42% (median 26%) after 2 weeks prolongation.[5] If RT delivery is shortened by 1 week, outcome improves by up to 9%.[6,7] Meta-analysis of trials comparing conventional RT to hyperfractionated and/or accelerated RT for head and neck cancer found a 5-year survival benefit of 3.4% that was higher with hyperfractionated radiotherapy (8%) than with accelerated radiotherapy (1.7–2%). Locoregional control benefit was 6.4% at 5 years.[8] Results similar to standard RT fractionation or better have been obtained with hypofractionated protocols.[3,9–13] Both methods of altered fractionation have been shown to offer some advantages. Standard, accelerated, hyper- and hypofractionated regimes are used in clinical practice.[14–18]

2. Aim

The goal of this study was to compare results of a hypofractionated, accelerated regime using 2.25 Gy fractions with results of standard and accelerated RT in patients with the same diagnosis and treated in the same center. Our hypothesis was that results would not differ, while utilization of radiotherapy equipment would be reduced.

3. Material and methods

Patients with squamous cell carcinoma of supraglottic or glottic larynx, age ≤75, WHO performance score 0–1, TNM (1987) T1-3, N0, M0, no history of another cancer (except for basal cell skin carcinoma) were enrolled prospectively. RT was selected as a single treatment modality. Exclusion criteria were uncontrolled and/or poor-risk serious medical co-morbidities that in the opinion of the treating physician were very likely to prevent the patient from completion of the RT course (for example: circulatory insufficiency, recent myocardial infarction, COPD with dyspnea at rest, renal insufficiency, active tuberculosis), tracheostomy done before oncological management, previous laser microsurgery of the larynx. The study endpoints were overall survival (OS), progression-free survival (PFS), treatment toxicity evaluated according to modified Dische scale[19] after RT at 4 weeks, 8 weeks (early toxicity) and at the last follow-up visit (late toxicity).

Results in this group (group H – hypofractionated accelerated RT – KBN 6 P05C 032 20 project) were compared to results obtained in the trial that was conducted earlier in the same centers and used the same set of clinical data (group A – accelerated RT, 196 patients and group S – standard RT, 199 patients, KBN 4 3004 94C/2008 project).[20]

3.1. *Dosimetry, treatment planning and fractionation*

Dosimetric measurements were performed according to ICRU recommendations.[21] Radiotherapy was delivered by Co-60 source to patient placed in supine position, with head fixed in a thermoplastic mask. CT imaging was used for multi-slice 2D planning with the Mevaplan system (Siemens).

In patients with T1–2 N0 glottic cancer, total dose of 63 Gy in 2.25 Gy fractions was delivered to the larynx only. In patients with T3 N0 glottic cancer and T1–3 N0 supraglottic cancer both the larynx and the neck lymph nodes (levels II–VI) were irradiated with 19 fractions of 2.25 Gy, then radiotherapy was delivered only to the larynx up to a total dose of 63 Gy. Table 1 presents fractionation in study and control groups.

Table 1 – Fractionation regime in study (hypofractionated) and control (accelerated, standard) groups.

	Group H	Group A	Group S
Number of patients	223	196	199
Fraction dose	2.25	2.0	2.0
Number of fractions	28	33	33
Total dose (Gy)	63	66	66
Total RT duration (days)	38	38	45

Total number of recruited patients with T1–3 N0 laryngeal cancer was 223. Patients with T3 tumors ($n = 18$) had fixation of the hemilarynx. Two patients terminated RT early, after 9 and 58.5 Gy. 85 (38%) patients had RT duration longer than planned. If RT course lasted up to 41 days, total dose remained unchanged. Thirteen patients had delays of more than 3 days that were caused by severe treatment toxicity, holidays, technical problems and patient's absence. Single fraction was added in 10 patients, 2 fractions in 1 and 3 fractions in 2 patients. 208 patients completed study according to the protocol. Table 2 summarizes clinical data.

3.2. *Endpoints and statistical methods*

Overall survival (OS) was the principal endpoint in this study. It was defined as time from date of patient's consent to participate in the trial to the date of death or the last follow-up observation.

Progression-free survival (PFS) is the second endpoint. In the study group and in control groups, the result of a clinical evaluation of loco-regional status 8 weeks after completion of RT served as reference. The PFS time was calculated from patient's trial entry date to the first failure: loco-regional recurrence, distant metastasis, death of any cause or last clinical observation.

Third endpoint is treatment toxicity evaluated according to the Dische scale.[19] Early toxicity was evaluated during RT, 4 and 8 weeks after completion of RT. Late toxicity was evaluated at each subsequent follow-up visit.

The OS and PFS were estimated using the Kaplan–Meier method. Log-rank test was used to compare survival curves. Chi-square test was used to compare acute and late toxic events. Cox proportional hazards regression model was used for multivariate analysis. All tests were performed at the .05 significance level.

The study protocol was approved by Ethical Review Committee in Cancer Center – M. Curie-Sklodowska Memorial Institute, ref. no. 45/2000.

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