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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.

Table 2 – Clinical data for study (H) and control (A, S) groups.

	Group H	Group A	Group S
Age–range (yrs)	37–75	31–75	37–75
Age–median (yrs)	60	58	61
Male	200 (90%)	170 (87%)	169 (85%)
Female	23 (10%)	26 (13%)	30 (15%)
WHO performance status			
0	190 (85%)	171 (87%)	177 (89%)
1	33 (15%)	25 (13%)	22 (11%)
Histological grade			
G1	63 (28%)	63 (32%)	68 (34%)
G2	92 (41%)	68 (35%)	71 (36%)
G3	20 (9%)	11 (5%)	11 (5%)
Undefined	48 (22%)	54 (28%)	49 (25%)
Tumor localization			
Glottis	159 (71%)	144 (73%)	148 (74%)
Epiglottis	61 (28%)	52 (27%)	51 (25%)
Upper and middle larynx	3 (1%)		
Tumor stage			
T1	112 (50%)	92 (47%)	93 (46%)
T2	90 (41%)	86 (44%)	85 (43%)
T3	18 (8%)	18 (9%)	20 (10%)
TIS	3 (1%)		
missing			1 (1%)
Duration of RTH			
According to plan	136 (62%)	104 (53%)	94 (47%)
Prolonged	85 (38%)	92 (47%)	105 (53%)
Total RTH dose	<63 Gy – 2 (1%) 63 Gy – 208 (93%) >63 Gy – 13 (6%)	<66 Gy – 1 (1%) 66 Gy – 174 (89%) >66 Gy – 21 (10%)	<66 Gy – 1 (1%) 66 Gy – 175 (88%) >66 Gy – 23 (11%)
Follow-up (median, min–max; months)	35 (4–72)	33 (3–65)	31 (3–73)

4. Results

There were no statistically significant differences in OS or PFS among the groups (Table 3 and Figs. 1 and 2).

In the H group complete regression of tumor was seen in 94% at 4 weeks and in 98% at 8 weeks, and partial regression in 5.5% and 2%, respectively. One patient had tumor progression at the 4 weeks visit, did not appear for the next visit and was lost to follow-up. Local recurrence of the tumor occurred in 17% of the group H patients, metastases to the neck lymph nodes in 3.6%, distant metastases in 2.3%. Six patients had local and regional recurrence, 1 had local recurrence and distant metastases.

OS and DFS by tumor stage, patient age, WHO performance status and tumor localization in the H group are presented in Table 4. Statistically significant difference in DFS was found between localization in the glottis or supraglottis subgroups. Location in supraglottis was associated with lower five-year DFS (54% vs. 82%).

Cox multivariate analysis was performed separately for group H subgroups with cancer of the glottis and cancer of the supraglottis because the tumor location variable did not meet the proportional hazard assumption. None of the analyzed variables had a significant impact on OS or DFS in supraglottis cancer subgroup. In the glottis cancer subgroup T3 stage had significant negative impact on OS and on DFS. Age ≥64 years was associated with worse OS. Negative impact of longer

Table 3 – Overall Survival and Progression Free Survival in study and control groups.

	Overall Survival		Progression Free Survival	
	3-year (95% CI)	5-year (95% CI)	3-year (95% CI)	5-year (95% CI)
Group H	90.5% (90.0–91.0%)	87.5% (81.5–93.5%)	77.0% (70.4–83.6%)	73.6% (66.2–81.0%)
Group A	87.1% (81.1–92.7%)	84.5% (78.1–90.1%)	77.2% (70.2–84.2%)	77.2% (70.2–84.2%)
Group S	89.7% (84.3–95.1%)	86.2% (77.8–94.6%)	71.6% (64.8–78.4%)	66.2% (57.2–75.2%)

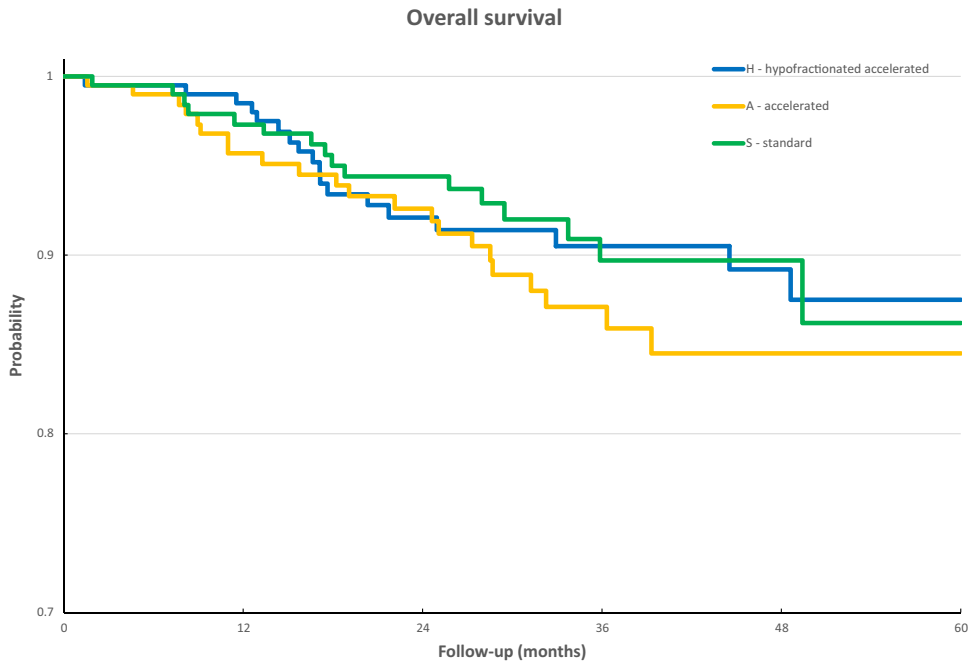

Fig. 1 – Kaplan–Meier graph for overall survival in study group (H), accelerated (A) and standard RT (S) groups.

than planned RT delivery on DFS did not reach statistical significance ($p = .055$). Results of the multivariate analysis are presented in Table 5.

Manifestations of acute radiation toxicity (any intensity) occurred in almost all patients in each group (H – 99.5%, A – 100%, S – 97%). Late toxicity manifestations of any intensity were observed in more than 90% of patients (group H – 92%, A – 95%, S – 91%). Frequency of acute and late toxicity in the study group (H) and in the control groups (A and S) is presented in Table 6.

5. Discussion

High actuarial 5-year OS and PFS values (87.5% and 73.6% respectively) achieved in this trial are very similar to those

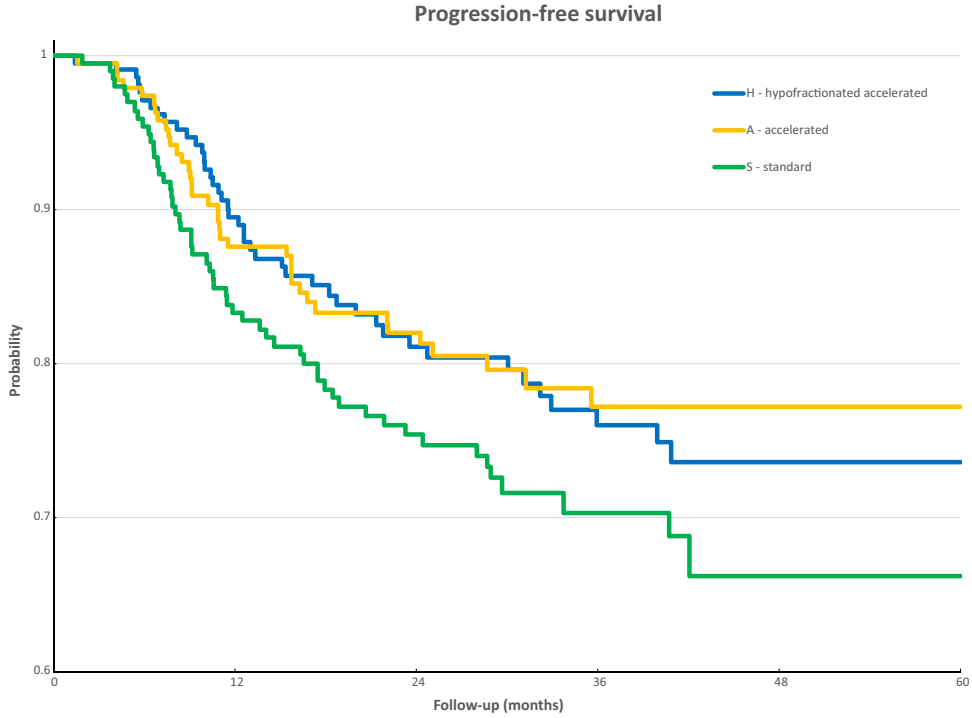

Fig. 2 – Kaplan–Meier graph for progression free survival in study group (H), accelerated (A) and standard RT (S) groups.

Table 4 – Survival by clinical factors in hypofractionated RT group (group H, n = 223).

Clinical factor	Overall Survival probability (SE)		Disease Free Survival probability (SE)	
	3 years	5 years	3 years	5 years
T				
T1	.948 (.023)	.930 (.029)	.799 (.046)	.799 (.046)
T2	.884 (.039)	.855 (.047)	.753 (.052)	.681 (.062)
T3	.857 (.094)	.643 (.198)	.646 (.128)	.646 (.128)
Age				
<55	.946 (.030)	.905 (.050)	.806 (.054)	.696 (.076)
55–64	.934 (.032)	.882 (.059)	.776 (.057)	.776 (.057)
>64	.833 (.052)	.833 (.052)	.730 (.059)	.730 (.059)
WHO PS				
0	.914 (.024)	.876 (.035)	.781 (.035)	.739 (.041)
1	.851 (.069)	.851 (.069)	.707 (.088)	.707 (.088)
Tumor localization				
Glottis	.926 (.024)	.903 (.033)	.832 (.033)	.817 (.036)
Supraglottis	.848 (.053)	.801 (.068)	.614 (.074)	.535 (.084)

Table 5 – Results of the multivariate analysis for risk of death and recurrence in glottic cancer subgroup receiving hypofractionated RT (*n* = 159).

	HR for death with 95% CI	*p*	3-years OS with SE	5-years OS with SE	HR for recurrence with 95% CI	*p*	3-years DFS with SE	5-years DFS with SE
T		.016				.010		
T1–T2	1		.930 (.025)	.930 (.025)	1		.822 (.037)	.822 (.037)
T3	3.16 (1.24, 8.05)		.429 (.310)	.429 (.310)	2.37 (1.23, 4.58)		.686 (.186)	.686 (.186)
Age		.044						
≤64	1		.928 (.040)	.928 (.040)				
>64	2.51 (1.03, 6.13)		.856 (.56)	.856 (.56)				
RT prolongation						.055		
No					1		.873 (.036)	.853 (.040)
Yes					2.26 (.98, 5.18)		.750 (.071)	.750 (.071)

reported by other authors.[12,18,22–25] In some reports these indicators reach 100%.[2,13,26] The publications on hypofractionated accelerated RT for larynx cancer present results in T1–T2 tumors while in our study T3 tumors were diagnosed in 8% of patients in the H group. In the subgroup of patients with T1–T2 tumors (92% of H group) 5-year OS and PFS were 90% and 74%, respectively. These results are not statistically significantly different from the results in the whole H group.

In our study there were no statistically significant differences in OS and PFS between the study and control groups. Yamazaki et al. published results of a randomized trial of hypofractionated (2.25 Gy) vs. standard (2.0 Gy) RT in patients

Table 6 – Frequency of acute and late toxicity manifestations in study group and control groups.

Toxicity (Dische grade ≥2)	Group H	Group A	Group S	*p* Value
Acute				
Painful swallowing	85%	65%	53%	.006
Dysphagia	58%	42%	28%	.0004
Mucositis	68%	70%	56%	.323
Late				
Dysphagia	3%	13%	9%	.003
Edema	12%	12%	11%	.97
Fibrosis	6%	7%	6%	.91
Skin teleangiectasias	12%	23%	11%	.008
Xerostomia	28%	44%	42%	.048
Deep tissue necrosis[a]	.5%	0%	0%	
Thyroid cartilage inflammation[a]	1%	2%	1.5%	.604
Thyroid cartilage necrosis[a]	0%	.5%	0%	
Ulceration of mucosa[a]	1%	.5%	4%	.02

[a] Present or absent (not graded).

with glottis cancer. There was a statistically significant difference in 5-year local control in favor of the hypofractionated group (92% vs. 67%).[13] Also, Yu et al. reported better results in a hypofractionated group (2.25–2.5 Gy) as compared to a standard 2.0 Gy fractionation.[25] Rudoltz et al. found that fraction dose ≥2.0 Gy was more effective for local control than doses <2.0 Gy.[27] Ermis et al. reviewed results of 10 published series of hypofractionated RT for T1 and T2 tumors and found 5-year local control of 61–89% in T2.[28] Our results do not demonstrate significant differences among standard, accelerated and hypofractionated groups.

Importance of treatment duration is stressed in publications reporting RT for cancer of the glottis and other head and neck cancers. Shorter RT with the same total and fraction doses as those used in conventional radiotherapy improves loco-regional control and DFS.[3,7,26–29] This conclusion is also supported by results of meta-analysis of phase III trials that concentrated mainly on accelerated hyperfractionated protocols, published by Bourhis et al.[5] Reduced total dose delivered over shorter time produced results similar to conventional RT.[15] Longer than standard treatment duration has a negative impact on outcomes of radiotherapy for head and neck cancer, with loco-regional control loss of 1.2% per day or 12–14% per week.[30]

Hypofractionated protocols are expected to cause more frequent late complications, while accelerated protocol should cause more acute toxicity, contrary to our results shown in Table 4.[13,31,32] In our study 2 out of 3 manifestations of early toxicity graded 2 or more according to the Dische scale were more frequent in the H group while 3 out of 9 late toxicity manifestations occurred more frequently in the A group. There were no significant differences in overall frequency of early and late toxicity of any grade among the A, H and S groups. Significance of these findings is limited due to the use of historical controls, which is a major drawback of our study. Participation of the same centers, use of the same criteria for clinical assessment and the same endpoints make comparisons among the H, A and S groups more reliable. Majority (17 out of 20) publications cited in our report and containing information on results of hypofractionated RT are retrospective case series. Kim et al. published results of treatment in T1–T2 glottic cancer with historical controls.[33] Two papers report results of randomized trials.[13,23] Due to differences in methodology, endpoints and follow-up duration the comparison of results is of a limited value. No difference in toxicity between standard and hypofractionated protocols was found in published reports of hypofractionated RT of the laryngeal cancer.[11,13,18,22,23,25] In majority of these reports a fraction dose of 2.25–2.5 Gy was used. The dose >3.0 Gy was linked to a higher complications rate,[13,34] but in a group of 200 patients reported by Gowda et al. in which 3.12–3.28 Gy doses were used for 3 weeks up to a total of 50–52.5 Gy, early and late toxicity were low.[22]

Reduced use of radiotherapy resources depends mainly on reduced number of RT sessions. Accelerated regimes that deliver the same number of fractions as conventional RT, reduce the treatment duration, but utilize the same amount of RT equipment time. The equipment is often the most scarce resource. Number of RT sessions used in our study protocol is reduced, thus freeing equipment for other patients. Similar conclusions have been proposed by other authors.[11,35]

In published reports number of patients treated with hypofractionated RT was limited and authors suggested a need for further research.[10,12,18,35] The group with hypofractionated RT reported in this paper is one of the largest published so far. More rigorous prospective studies could be considered to compare fractionation and timing of RT in the larynx and other head and neck patients and to provide stronger evidence, but published results quite consistently demonstrate that RT using fraction dose of 2.25–2.5 Gy delivered 5 days per week up to a total dose of 52–65 Gy gives the same or even better locoregional control than standard RT. Such conclusion is in agreement with conclusions of van der Voet et al. who found that 2.4 Gy fraction and a total dose of 60 Gy resulted in optimal disease control and the lowest long term toxicity.[34]

6. Conclusions

The results of hypofractionated accelerated RT protocol using fraction dose of 2.25 Gy and total dose of 63 Gy in 208 patients with cancer of the larynx were not significantly different from the results in the control groups treated with accelerated and with standard RT. These results are similar to those obtained in published studies of hyperfractionated, hypofractionated and standard protocols. The protocol used in this study allows for delivery of RT within 5 weeks with reduced use of the radiotherapy equipment, without increasing early and late radiation toxicity.

Conflicts of interest

None declared.

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