The impact of conventional or hypofractionated radiotherapy on voice quality and oncological outcome in patients with early glottic cancer

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Abstract. The hypothesis being tested in this study is that hypofractionated radiotherapy is well tolerated and not lower in terms of oncological outcome than conventional radiotherapy. Forty patients with histologically proven glottic cancer were included in the analysis. Twenty-two were treated by hypofractionated radiotherapy (3D-HFRT) (25 fractions of 2.4 Gy delivered daily to a total dose of 60 Gy). This group was retrospectively compared to 18 subjects who met the same inclusion criteria and who were treated with conventional radiotherapy (3D-CRT) (33 fractions of 2 Gy delivered daily to a total dose of 66 Gy). One year after RT treatment in 10 patients (5 in the Arm-1 and 5 in the Arm-2) mild dysphonia persisted. The other patients achieved a complete recovery of the overall quality of voice with no significant difference documented between the two groups. At 3 years the local control rate was 100% for the patients treated with hypofractionated radiotherapy and 96% for the patients treated with conventional regimen. The statistical analysis did not show any significant difference in local control between the two groups (p=0.45). No significant acute and late toxicity was documented in both groups. Subjects with early glottic cancer seem to experience comparable levels of morbidity irrespective whether they were treated by hypofractionated or conventional conformal therapy without any worsening of the tumor local control. Thus, we provide clinical evidence to justify trends already emerging toward hypofractionated regimens in early glottic cancer.

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Introduction

Radiation therapy (RT) and endoscopy laser surgery (ELS) are established treatment modalities for early glottic cancer. These treatments offer the same results but their comparative benefits are debated. Even though ELS is quicker, which reduces cost considerably, many institutions prefer to use radiotherapy (1-5). This choice depends on the fact that the voice function and quality are better preserved after treatment (6-9). Starting from this evidence many efforts have been made to find a better RT therapeutic plan. Accelerated fractionation RT has considerable benefits in terms of treatment duration and cost compared with conventional fractionation methods (1). Furthermore, the increased single dose radiation and shortened treatment time may improve the local control (5). Various types of fractionation methods are performed in clinical practice but an optimal fractionation protocol has not yet been established. The principal goal of an oncology treatment is the complete eradication of the cancer but regard the early glottic cancer another essential aspect is the normal voice preservation. If RT or ELS permit an efficient disease local control, questionable are the effects on the voice quality that has to be consider a relevant factor to take into account when evaluating the results. The voice is important for social interaction and its quality is essential for emotional expression, for this reason is necessary to use the better treatment able to preserve voice functions (10). Objective or semi-objective measurements and analysis have been developed to evaluate the disease local control and the voice quality. Perceptual analysis of dysphonia (GRBAS), acoustic and spectrographic analysis, aerodynamic efficiency analysis, patient self-perception analysis (Voice Handicap Index) are an example of the most used system of voice quality. The hypothesis being tested in this study is that hypofractionated radiotherapy is well tolerated and not lower in terms of oncological outcome than conventional radiotherapy. We compared these two treatment regimens in terms of efficacy, safety and voice quality in a population of subjects suffering from early glottic cancer. Results from the objective and subjective voice quality analysis as well as the oncological outcome were measured.

Table I. Stage and treatment parameters.

Variable	No. of patients (%)
Stage	
Ia	23 (57.5)
Ib	17 (42.5)
Field size (cm^3)	
≤36	19 (47.5)
>36	21 (52.5)
Time (days)	
≤30	22 (55)
>30	18 (45)

Table II. The Voice Handicap Index.

Instructions: these are statements that many people have used to describe their voices and the effects of their voices on their lives. Circle the response that indicates how frequently you have the same experience: never, almost never, sometimes, almost always, always.

F1	My voice makes it difficult for people to hear me.
F2	I run out of air when I talk.
F3	People have difficulty understanding me in a noisy room.
P4	The sound of my voice varies throughout the day.
F5	My family has difficulty hearing me when I call them throughout the house.
F6	I use the phone less often than I would like.
E7	I am tense when talking with others because of my voice.
F8	I tend to avoid groups of people because of my voice.
E9	People seem irritated with my voice.
P10	People ask, 'What's wrong with your voice?'
F11	I speak with friends, neighbors, or relatives less often because of my voice.
F12	People ask me to repeat myself when speaking face-to-face.
P13	My voice sounds creaky and dry.
P14	I feel as though I have to strain to produce voice.
E15	I find other people do not understand my voice problem.
F16	My voice difficulties restrict my personal and social life.
P17	The clarity of my voice is unpredictable.
P18	I try to change my voice to sound different.
F19	I feel left out of conversations because of my voice.
P20	I use a great deal of effort to speak.
P21	My voice is worse in the evening.
F22	My voice problem causes me to lose income.
E23	My voice problem upsets me.
E24	I am less outgoing because of my voice problem.
E25	My voice makes me feel handicapped.
P26	My voice 'gives out' on me in the middle of speaking.
E27	I feel annoyed when people ask me to repeat.
E28	I feel embarrassed when people ask me to repeat.
E29	My voice makes me feel incompetent.
E30	I am ashamed of my voice problem.

Materials and methods

From May 2000 to October 2008, 40 patients with T1 squamous cell carcinoma of the true vocal cords were irradiated with curative intent. Male patients, with an age from 50 to 85 years (median 67 years) and with a Karnofsky performance score ≥80% were analysed. The median follow-up was 36 months. Patients were staged according to the American Joint Committee on Cancer system (AJCC), based on findings at indirect or direct laryngoscopy with histological confirmation of diagnoses. In 23 patients the tumor involved one vocal cord (cT1a) while in 17 patients involved two vocal cords with or without the anterior commissure (T1b). No patient presented with clinically or histologically positive neck lymphadenopathy. Patient characteristics and treatment-related parameters are shown in Table I. All patients received continuous-course irradiation using once-a-day fractionation with 5 fractions per week and were treated with megavoltage equipment using 6 MV photons. Two fractionation groups were identified with respect to daily fraction size and total dose. Arm-1 consisted of 18 patients who received a total dose of 66 Gy in 33 daily fractions of 2.0 Gy. Arm-2 consisted of 22 patients who received a total dose of 60 Gy in 25 fractions of 2.4 Gy. Field arrangement included parallel opposed lateral fields with appropriate wedges. Field size range was 26-76 cm^2 (median 36 cm^2). 8 patients in Arm-1 and 11 patients in Arm-2 had ≤36 cm^2, 10 patients in Arm-1 and 11 patients in Arm-2 had ≥36 cm^2. Patients were treated in supine position and were immobilized with termoplastic mask. In all patients we evalued voice quality and vocal function before, 6, 12, 24 and 36 months after radiotherapy. Our examination protocol included: perceptual voice (analysis of dysphonia) and patient self-perception analysis (Voice Handicap Index). During the treatment all patients were visited every day. An evaluation of the larynx respiratory space was performed every two weeks through a laryngoscopic examination.

Perceptual analysis of dysphonia (GRBAS). Perceptual analysis of dysphonia was performed using the GRBAS scale (10,11). All patients were recorded speaking the phonetically balanced 'rainbow passage' and the recordings were analyzed by two speech and language therapists (12,13) that classified each case from 0 to 3 (0, normal; 1, mild; 2, moderate; 3, severe). The severity of hoarseness is quantified with the parameter G (grade), which represents overall voice quality. B (breathness), audible impression of turbulent air leakage through an insufficient glottic closure, which may include short aphonic moments (unvoiced segments). R (roughness or harshness), audible impression of irregular glottic pulses, abnormal fluctuations in F0. A (asthenicity), impression of weakness in the spontaneous phonation, hypokinetic or hypofunctional voice. S (strain, vocal tension), auditive impression of excessive force or tension associated with spontaneous phonation (10).

Patient self-perception analysis (Voice Handicap Index). The Voice Handicap Index (VHI) is a valid self assessment questionnaire that includes 30 questions covering three domains: functional, physical and emotional; issues related to daily life (5 point rating scale). The total score of 30 questions has a range from 0 to 120 (7,14,15). We classified the vocal disability in mild (<30), moderate (31-60), severe (61-90) and very severe (91-120) (Table II). Following the treatment, patients were followed up every 3 months for the first and second year than every 6 months for the next three years and annually thereafter. The treatment parameters evaluated were: stage, field size, daily fraction size, total dose, overall treatment time, complications and voice quality post-treatment. Toxicity was scored using the evaluated Radiation Therapy and Oncology Group (RTOG) scale.

Statistical methods. Adjusted p-values of p=0.05 can be interpreted as statistically significant test results. All tests were two-sided. Continuous variables were presented as means, medians and standard deviation (SD). Local control and global survival were valuated with the Fisher test, the toxicity was assessed using the RTOG scale. The percentage of dysphonia (GRABS scale) between the two groups of treatment was mesured using the χ^2 test while the cochran test was used to compare the GRABS scale between the pre- and post-radiotherapy dysphonia. VHI differences between the two groups of treatment was assessed using the t-test while the Anova test was used to compare the VHI between the pre- and post-radiotherapy condition. All statistical analyses were performed using the SPSS® statistical analysis software package, version 10.0.

Results

Analysis of dysphonia. We investigated vocal performance before and after radiotherapy treatment. Before RT, 11 patients (Arm-1) and 13 (Arm-2) presented mild dysphonia (G-grade), 6 (Arm-1) and 9 (Arm-2) showed a moderate dysphonia while one patient (Arm-1) presented severe dysphonia. One year after RT treatment in 10 patients (5 in the Arm-1 and 5 in the Arm-2) persisted mild dysphonia. The other patients achieved a complete recovery of the overall quality of voice. The same results were analyzed evaluating the other parameters of the GRABS scale (Table III). After one year from RT treatment, the dysphonia was significantly improved in all patients and remained stable in the next 2 years. All patients before RT showed an overall voice quality deteriorating while the vocal performance was strongly improved at 36 months after irradiation. A significant difference was found between pre- and post-radiotherapy for both groups (Table III).

Voice Handicap Index. Forty patients completed the VHI questionnaire. All variables were statistically decreased from pre- to post-treatment (Table IV). No significant difference between the first and second arm was documented.

Local control, acute and late complications. After 3 years of follow-up the local control rate was 100% for the patients treated with >2 Gy/fraction and 96% for the patients treated with 2 Gy/fraction. The statistical analysis did not show any significant difference in local control between the two groups (p=0.45). No lymph node recurrence and systemic metastasis were documented. No patient required interruption of treatment due to acute toxicity in both groups. About the acute complications, during the treatment one patient showed dysphonia grade 3 (Arm 1), 18 dysphonia grade 2 (6 in the Arm-1 and 12 in the Arm-2) and 21 dysphonia grade 1 (11 in the Arm-1 and 10 in the Arm-2). After 3 months dysphonia grade 1 disappeared in 12 patients (5 in the Arm-1 and 7 in the Arm-2) (Fig. 1). No statistically significant differences in the two groups of patients were found (p=0.26 during RT, p=0.95, 3 months later). No patients suffered of dysphagia superior to grade 2, 15 showed dysphagia grade 2 (8 Arm-1

Table III. GRABS comparision of results obtained three years after radiotherapy in Arm-1 and 2.

	0	1	2	3
GRABS Arm-1				
G pre-RT	0/18	11/18	6/18	1/18
1 year after-RT	13/18	5/18	0/18	0/18
3 years after-RT	10/15	5/15	0/15	0/15
R pre-RT	1/18	12/18	5/18	0/18
1 year after-RT	15/18	3/18	0/18	0/18
3 years after-RT	12/15	3/15	0/15	0/15
A pre-RT	1/18	12/18	6/18	0/18
1 year after-RT	13/18	5/18	0/18	0/18
3 years after-RT	12/15	3/15	0/15	0/15
B pre-RT	1/18	14/18	4/18	0/18
1 year after-RT	14/18	4/18	0/18	0/18
3 years after-RT	12/15	3/15	0/15	0/15
S pre-RT	0/18	14/18	3/18	1/18
1 year after-RT	15/18	3/18	0/18	0/18
3 years after-RT	13/15	2/15	0/15	0/15
GRABS Arm-2				
G pre-RT	0/22	13/22	9/22	0/22
1 year after-RT	17/22	5/22	0/22	0/22
3 years after-RT	11/15	4/15	0/15	0/15
R pre-RT	2/22	16/22	4/22	0/22
1 year after-RT	18/22	4/22	0/22	0/22
3 years after-RT	12/15	3/15	0/15	0/15
A pre-RT	1/22	17/22	4/22	0/22
1 year after-RT	18/22	4/22	0/22	0/22
3 years after-RT	12/15	3/15	0/15	0/15
B pre-RT	0/22	18/22	4/22	0/22
1 year after-RT	17/22	5/22	0/22	0/22
3 years after-RT	12/15	3/15	0/15	0/15
S pre-RT	0/22	17/22	5/22	0/22
1 year after-RT	18/22	4/22	0/22	0/22
3 years after-RT	13/15	2/15	0/15	0/15

Table IV. Means, medians, standard deviations (SD) for participants to VHI questionnaire at pre-treatment and post-treatment.

	Pre-treatment				Post-treatment (1 year)				Post-treatment (3 years)				
Variable	No.	Mean	Median	SD	No.	Mean	Median	SD	No.	Mean	Median	SD	P-value
Arm-1													
Functional	18	15.4	15	2.5	18	7.5	7.5	5	15	12	11	2.7	<0.0001
Physical	18	15.2	14.5	3	18	7.6	7	4.2	15	11.7	1	2.9	<0.0001
Emotional	18	13.7	12.5	3.5	18	7.5	7	3.9	15	11	10	2	<0.0001
Global	18	44.3	42	8.5	18	23.2	23	12.4	15	34.6	33	7.3	<0.0001
Arm-2													
Functional	22	15.5	15	2.4	22	7.8	8	5	15	11.8	12	2.7	<0.0001
Physical	22	14.6	14.5	2.5	22	7.8	7.5	4.7	15	11.7	12	2.6	<0.0001
Emotional	22	13.8	13	2.7	22	7	7	5.2	15	11.2	11	2.8	<0.0001
Global	22	44	42.5	7	22	22.5	22.5	14.5	15	34.8	34	7.7	<0.0001

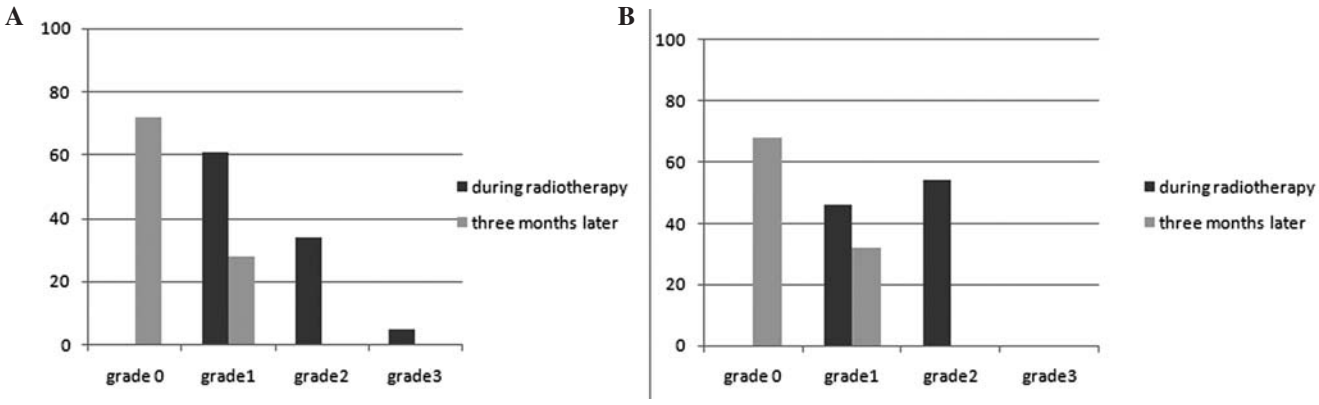

Figure 1. Impact of conventional (Arm-1) (A) and hypofractionated (Arm-2) (B) radiotherapy on dysphonia.

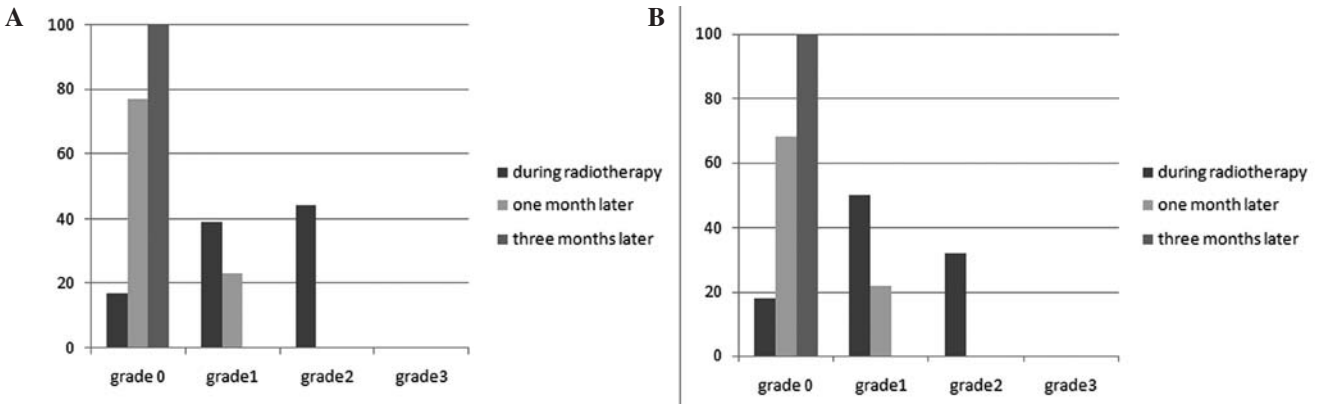

Figure 2. Impact of conventional (Arm-1) (A) and hypofractionated (Arm-2) (B) radiotherapy on dysphagia.

and 7 Arm-2) and 7 dysphagia grade 1 (3 in the Arm-1 and 4 in the Arm-2) (Fig. 2). Overall symptomatology disappeared within the first 3 months from treatment. The statistical analysis did not show any significant difference between groups during the RT (p=0.70) or 3 months later (p=0.86). Eight patients (Arm-2) showed erythema of grade 2, 10 patients (Arm-1) and 8 (Arm-2) showed cutaneous toxicity of grade 1. Overall erythema disappeared one month after treatment. No difference in both groups was noted. Four patients (2 in the Arm-1 and 2 in the Arm-2) showed edema of the vocal cords of grade 2 during therapy while 10 patients (Arm-1) and 13 (Arm-2) of grade 1 (Fig. 3). After 3 months

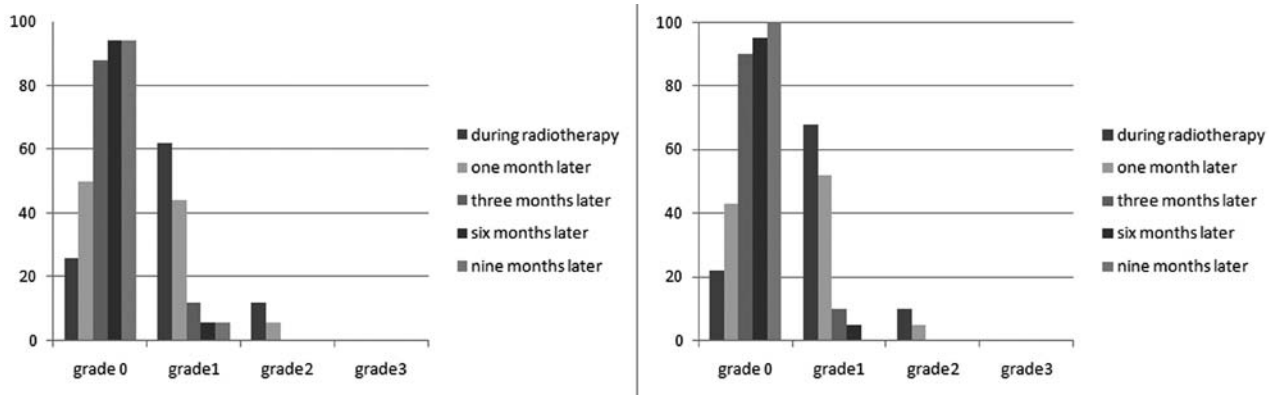

Figure 3. Impact of conventional (Arm-1) and hypofractionated (Arm-2) (B) radiotherapy on edema of the vocal cords.

4 patients (2 Arm-1 and 2 Arm-2) showed edema of grade 1. No difference in both groups was documented during RT (p=0.64) or 3 months later (p=0.92). No significant late toxicity was observed in both groups.

Discussion

Radiotherapy is a curative therapy for the early glottic cancer and contrary to surgery guarantees a good preservation of the voice. Despite the relative safety, RT induces abnormalities in voice quality impairing the quality of social life, thus, voice conservation and the local disease control are both essential. Some clinical results have demonstrated the importance of reducing irradiation time and increasing the daily dose in improving tumour control. This can be achieved by hyper- or hypofractionation although there are limits to the multiple daily fraction/short irradiations. To speed up the irradiation time by hypofractionation is a relevant alternative to hyperfractionated regimens. Nevertheless, there are concerns about the late toxicity produced by this treatment modality. Late normal tissue reactions are more dependent on the dose per fraction than acute reactions. Therefore, although there is no doubt that hypofractionation offers major potential advantages to patients and to the economy of health systems, their development should not be at the expense of a lower likelihood of tumour control as well as of an unacceptable late toxicity (1,3,5,16,17). Hypofractionated treatment benefits depend on the fact that these cancer cells, characterized by a slow proliferation, during radiotherapy increase the proliferation rate becoming more radiosensitive (18-20). In this study we analyze the voice quality and disease local control in patients with cT1a squamous cell carcinoma of true vocal cords treated with conventional or hypofractionated radiotherapy. In order to study the voice quality we used the voice handicap index as objective measurement and the analysis of dysphonia as semi-objective measurement. We chose these systems because they have already been validated, reliable, simple and rapidly applicable. All patients were investigated before radiotherapy and 6 months to 3 years after radiotherapy. Questionnaires at each follow-up visit and clinical examination with video-laryngoscopy were performed. We also analyzed the dysphonia during treatment and three months after, using the RTOG scale. We found that the overall voice quality returned to normal levels in 75% of patients 12 months after RT while modest modifications were observed in 25% of patients. There were not differences in the voice recovery among patients treated with conventional or hypofractionated RT. The patients revealed a functional, physical and emotional improvement of the vocal performance after RT treatments starting from the 6th to the 12th month. The improvement remained stable during the follow-up. Several studies have analyzed the effects on voice quality of conventional or hypofractionated RT in patients with early glottic cancer (7,10,18) using different approach such as the acoustic, aerodynamic analysis, auditory-perceptual voice measures and serial electroglottographic methods. In line with these studies we showed the safety of hypofractionated RT treatment in early glottic cancer patients using evaluation methods easier, less expensive and more standardized. Particularly, two different schedules of treatment, conventional and hypofractionated, allowed a good preservation of the voice quality. In addition, both regimes of radiation therapy achieved similar results in terms of local control and complications. We will be able to get further information with the raising of the follow-up, because further improvements can be achieved in the years following radiotherapy. Our results should be analyzed in the light of the potential limitations that the study has. The oncological data should be interpreted cautiously since the median follow-up in both groups may be regarded as short for a disease whose natural history can spread across decades. Given time, it is therefore possible that the observed local tumor control could not reflect the real oncological effectiveness of the treatments. Finally, the retrospective nature of this study may have introduced methodological biases and this should be taken also into consideration. However, the use of a pre- and post-test experimental design may have partially mitigated these biases allowing us to maintain good statistical power.

With these limitations, men with early glottic cancer seem to experience comparable levels of morbidity quite apart from whether they received hypofractionated or conventional conformal therapy. These results were achieved without any worsening of the local tumor control. We provide some clinical evidence to justify trends already emerging toward hypofractionated regimens in early glottic cancer. Further studies and longer follow-up will be required to confirm these results.

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