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CLINICAL INVESTIGATION **Head and Neck**

CARCINOMA OF THE LARYNX TREATED WITH HYPOFRACTIONATED RADIATION AND HYPERBARIC OXYGEN: LONG-TERM TUMOR CONTROL AND COMPLICATIONS

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Purpose: To evaluate the long-term outcome with respect to local control, survival, and complications in a cohort of patients with locally advanced laryngeal carcinoma treated with hypofractionated radiation and hyperbaric oxygen at 4 atmosphers of pressure (HBO-4).

Methods and Materials: Between January 1970 and August 1982, 45 patients with locally advanced carcinoma of the larynx were treated with primary radiation using a unique hypofractionated schedule of 2 fractions of 11 Gy separated by 21 days, with concomitant HBO-4 during each radiotherapy session. To avoid seizures, discomfort and other complications of HBO-4, each session was performed under general anesthesia. All patients had pathologically confirmed squamous cell carcinoma of the glottic (23) or supraglottic larynx (22) and were staged as follows: T2-5, T3-24, T-4-16; N0-26, N1-4, N2-13, N3-1. Patients were treated with opposed lateral wedged fields of 4-6MV photons, with a median field size of 5.5 × 9.75 to a total median dose of 22.5 Gy.

Results: As of February 1998, follow-up was complete on all but one patient, who relocated to another country after 8 years. Complete clinical responses were observed in 39 (87%) of the cases. The 10-year local control rate for all 45 patients was 58%, and local control for the complete responders was 69%. Three patients underwent laryngectomy for complications and were found to have no pathological evidence of disease in the laryngectomy specimen. The 10-year survival of the overall population was 27%. The 10-year voice preservation rate for the the 39 complete responders was 55%. Acute mucosal and skin reactions were modest and acceptable. Significant late complications occurred in 14 patients consisting of severe fibrosis, necrosis, pharyngeal fistula, with 3 patients requiring laryngectomy for complications. The actuarial rate of severe complications at 5 years was 42%.

Conclusions: The response rate and long-term tumor control rate obtained with this treatment program were comparable to more protracted radiation schedules with or without systemic chemotherapy. The complication rate was high resulting in an adverse therapeutic ratio. The radiobiologic interpretation of this clinical data, and implications for hypoxia directed therapy, are discussed. **© 1999 Elsevier Science Inc.**

Larynx cancer, Hyperbaric oxygen, Radiation therapy, Hypofractionation.

INTRODUCTION

The potential clinical importance of the oxygen effect as a cure-limiting factor in clinical radiotherapy was recognized by the landmark observations of Thomlinson and Gray in 1955. Since that time, a multitude of strategies have been devised to overcome the radioresistance of viable hypoxic cells (1–17). These include measures to increase the partial pressure of oxygen at the tumor cells, to sensitize hypoxic cells with electron affinic drugs, to treat with high LET radiation, and to target hypoxic cells with specific cytotoxins. Although none of these strategies has achieved general acceptance into clinical practice, a recent meta-analysis of trials designed to overcome tumor hypoxia using either hypoxic cell sensitizers or hyperbaric oxygen showed a highly significant benefit in terms of both local control and survival (11) with the majority of benefit observed in patients with squamous cell carcinoma of the head and neck.

Conceptually, the simplest method of overcoming the resistance of hypoxic cells is to treat patients while they breathe hyperbaric oxygen and thereby increase the diffusion range of oxygen from capillaries. From the 1950s to the 1970s, a number of clinical trials were conducted around the world to test this strategy (1,6,7,13–15,17). In almost all cases, these trials used abbreviated fractionation schedules, mainly because of the logistic problems associated with pressurization and treatment in a hyperbaric chamber. However, radiobiological arguments were also advanced that hypofractionation combined with the highest possible oxygen pressure would increase the efficacy of hyperbaric

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treatment (15). It must be realized that these predictions and the treatment schedules derived from them were made before recognition of the dissociation between severity of acute and late normal tissue reactions with changes in dose fractionation (18).

Within the spectrum of hyperbaric treatment schedules, the Peter MacCallum Cancer Institute (PMCI) experience is unique in that patients were treated at a pressure of 4 atmospheres absolute (ATA, gauge pressure 45 psi). This has theoretical advantages over treatment at 2–3 ATA as used in other centers. Because of the risk of convulsion and otic barotrauma at 4 atmospheres, PMCI patients were treated under general anesthesia and had bilateral myringotomy prior to treatment. For patients with squamous cell carcinomas of the head and neck, a fractionation schedule of two fractions of 10.5 to 11.5 Gy spaced 21 days apart was used. A preliminary report of the results achieved in patients with cancers of the oral cavity, pharynx and larynx was published in 1972 (17). This review was undertaken to assess the long-term results of treatment of patients with advanced laryngeal cancer with specific reference to the rates of tumor control, voice preservation, and late normal tissue injury resulting from the extreme form of hypofractionation used.

METHODS AND MATERIALS

The hyperbaric therapy unit at the Peter MacCallum Cancer Institute was opened in 1961 and closed in August 1982. For the current study, patients treated in the hyperbaric unit from January 1970 through August 1982 were reviewed. All patients during this time interval were treated with an identical treatment program of two high dose fractions over 21 days under hyperbaric conditions. From the hyperbaric unit log book, we identified all patients treated in the hyperbaric unit who carried the diagnosis of carcinoma of the larynx. In an effort to assess a relatively homogeneous patient population, the current analysis was limited to patients with primary advanced laryngeal carcinoma treated with exclusive radiation without prior surgery. Those patients with primary hypopharyngeal lesions with laryngeal involvement were excluded from analysis. Patients with primary laryngeal carcinoma treated postoperatively and those treated for recurrent disease following surgery were also excluded from analysis. Included in the current analysis are 45 patients with the diagnosis of advanced carcinoma of the larynx treated with primary radiation therapy in the hyperbaric unit. Since the majority of early stage cancers were treated with more protracted radiation schedules (without hyperbaric oxygen) and the majority of advanced laryngeal carcinomas were treated surgically with or without postoperative therapy, this sample represents a small proportion of the overall larynx cancer population seen at the institution during this time interval. The T Stage and N Stage distribution of the patient population, as well as the overall characteristics of the patient population, are summarized in Tables 1 and 2 (1). All patients had locally advanced disease. The four patients with Stage II, T2N0 disease all had bulky lesions. Although there were no strict selection criteria, patients were generally offered this treatment with the understanding that they had a low probability of cure with conventional radiation therapy and, if the hyperbaric program failed to control the disease, salvage laryngectomy would be necessary (19). There were no strict age criteria or performance status criteria, however, all patients had to be considered fit enough to undergo general anesthesia for each hyperbaric session.

Table 1. Larynx patients: T Stage/N Stage distribution

		N Stage				
		N0	N1	N2	N3	Total
T Stage	T2	4	0	0	1	**5**
	T3	15	3	6	0	**24**
	T4	7	2	7	0	**16**
	Total	**26**	**5**	**13**	**1**	**45**

Patients were screened by the treating physicians in the hyperbaric unit and underwent routine blood work including complete blood count, chemistry profile, and chest x-ray. All patients underwent examination under anesthesia with biopsy and had histologically confirmed squamous cell car-

Table 2. Larynx patients Characteristics ($n = 45$)

	Mean	Range
Age	62.8	38–82
Hemoglobin	14.0	9–17.3
	Number	%
Histology		
Squamous	45	100
Gender		
Male	39	86.7
Female	6	13.3
Site		
Glottic	23	51.1
Supraglottic	22	49.9
ECOG status		
0	32	71.1
1	13	28.9
T Stage		
T2	5	11.1
T3	24	53.3
T4	16	35.6
N Stage		
N0	26	57.8
N1	5	11.1
N2	13	28.9
N3	1	2.2
M Stage		
M0	44	97.8
M1	1	2.2
Stage		
II	4	8.9
III	15	33.3
IV	26	57.8

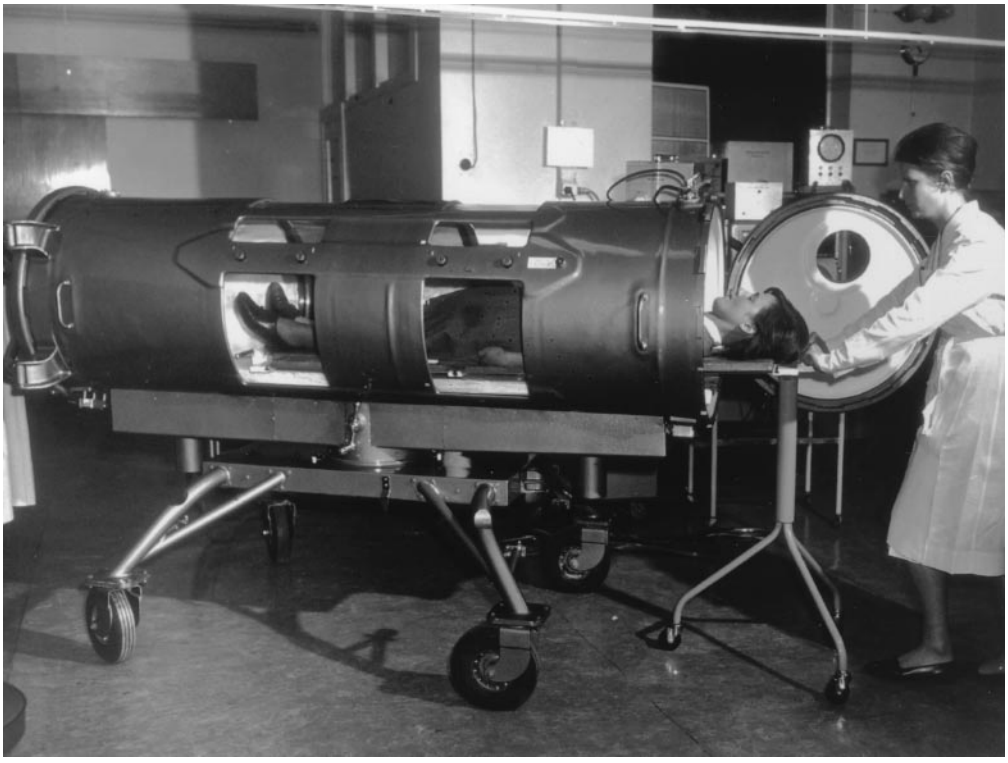

Fig. 1. Original hyperbaric unit used for patients in this study.

cinoma of the larynx. A laryngogram was a routine component of the staging workup. CT scanning was not routinely performed during this time interval (20).

Once patients were completely screened and staged as noted, they were scheduled for barotherapy. All patients were treated with 4 or 6 MeV linear accelerators. Scatter from the walls of the chamber and transmission factors through the chamber were accounted for in the dosimetric planning.

Patients were admitted to the hospital on the night before barotherapy, and sedated with 100 mg Nembutal orally. All patients were gowned in regulation non-flammable pajamas for each session. Phenergan was administered 4 hours prior to the barotherapy session and Omnopon and Scopolomine were administered 2 hours prior according to age, weight and general medical condition. At the time of treatment, the patient was anesthetized with 1% sodium pentobarbitone at 3–6 mg/kg, and intravenous pethidine or heroin. The throat was sprayed with 4% xylocaine and an endotracheal tube passed to secure the airway. This anesthetic program does not result in respiratory paralysis, thus allowing patients to breathe spontaneously without positive pressure ventilation. A bilateral myringotomy was performed on each patient. While under anesthesia, the patient was transferred to the simulator for a treatment planning film and marking. Patient contours were routinely obtained, and compensating wedges and filters were used as necessary to obtain a homogeneous dose distribution. After being accurately planned and marked in the simulator, the patient was transferred in the treatment position to the pressure vessel, which was flushed with pure oxygen. Electrocardiogram and thermistor probes were attached to the patient. The patient was rapidly pressurized at a rate of 15 pounds per minute to 45 psi (4 atmospheres) and allowed to "soak" in oxygen for 25 minutes. The chamber was then brought to the radiation treatment unit and radiation was administered through the perspex sections of the hyperbaric unit. A photograph of the hyperbaric unit is shown in Figure 1. Each field was treated in accordance with the dose specified, and the patient was brought back to the barotherapy unit for decompression. At the completion of the procedure, the patient underwent a post anesthesia check and was returned to the ward for post anesthesia and nursing care. Patients were discharged on the following day and readmitted for the second barotherapy treatment 21 days later.

For the current series, all patients were treated on days 0 and 21 to a total median dose of 22.5 Gy administered in two fractions. Field sizes for the first and second dose were identical. It is notable that the field sizes used in this treatment program were relatively small (average size 5.5 cm by 9.5 cm) in comparison to current standards for patients with advanced laryngeal cancers, and the posterior field edge did not encompass the spinal cord or posterior neck nodes. Chemotherapy was not routinely used, although two patients did receive concomitant hydroxyurea. Treatment characteristics of the patient population are summarized in Table 3. All patients except for two received both treatments under hyperbaric conditions. One patient experienced a pulmonary embolus after the first treatment and underwent the second treatment in air. Due to servicing of

Table 3. Larynx patients treatment characteristics ($n = 45$)

	Number	%
Hyperbaric oxygen		
1st treatment	44	97.8
2nd treatment	44	97.8
Chemotherapy (hydroxyurea)	2	4.4
Field arrangement		
Opposed laterals	45	100
Low neck field added	6	13.3
	Median	Range
Radiation time (days)	21.0	18–29
Dose (Gy)	22.5	19.8–25.5
Field size (laterals)		
Width (cm)	5.5	4.0–10.0
Length (cm)	9.5	5.5–13
Field size (low neck)		
Width (cm)	8.25	4–16
Length (cm)	8.75	4–14.5

the hyperbaric unit, one patient had his first treatment in air, but received the second treatment in the hyperbaric unit.

Patients were followed on a regular basis by the physicians in the hyperbaric unit, as well as by their referring otolaryngologist. Patients were seen on at least a monthly basis for the first several months following treatment and quarterly thereafter.

For the current study, the medical record was reviewed in detail for all acute and chronic normal tissue reactions, tumor response, local, regional, and distant metastasis and long-term survival. Data were extracted from the medical record, which included all detailed notes from the hyperbaric unit, as well as correspondence from referring physicians. In addition to the medical record, the hyperbaric unit maintained a normal tissue acute reactions log, which was reviewed to additionally document the acute normal tissue reactions. Acute and chronic normal tissue reactions were retrospectively categorized in accordance with current ECOG/RTOG criteria (21). Patients were scored as complete clinical responders if they had no clinical evidence of persistent or recurrent tumor within three months of treatment. Patients with less than a complete response over this time interval, but in whom there was no evidence of tumor progression, were scored as partial responders. Patients with clinical or pathological evidence of persistent disease at any time were scored as local failures from time zero for actuarial calculations. Patients with clinical and/or radiographic evidence of regional and/or metastatic disease were scored accordingly. Patients experiencing regional failure outside the radiation therapy field were scored as marginal relapses.

As noted previously, the complete patient record was reviewed for evidence of acute and chronic complications. Patients were scored as having severe complications if they had any evidence of necrosis of soft tissue, bone or cartilage, fistula formation, or severe pharyngeal fibrosis requiring surgical intervention and/or tube feeding. In those cases

Table 4. Acute reactions

	Number	Percent
Epidermitis		
G II	15	33.3
G III	11	24.4
Mucositis		
G II	24	53.3
G III	16	35.6

Grading of complications is based on current RTOG/ECOG criteria.

in which necrosis and/or fistula formation occurred simultaneously with recurrent disease, patients were scored as having recurrent disease rather than a severe complication, as it was not possible to determine in this retrospective review whether the necrosis and/or fistula was related to tumor recurrence or normal tissue reaction. All patient data extracted from the medical record and tissue reactions log were entered into a computerized database using the PRODAS Database Management System (22). Survival curves were calculated by the life table method with differences in survival curves compared by the Mantle Haensel chi square statistical test (23). Differences between categorical variables were tested using the Pearson chi-square statistical test.

RESULTS

As of February 1998, follow-up was complete on all but one patient who was lost to follow-up 8 years after his initial diagnosis when he relocated to another country.

Treatment tolerance and normal tissue reactions

Treatment was tolerated well, and with the exception of the two patients who did not receive one of their treatments under hyperbaric conditions, all patients received both hyperbaric treatments without adverse events, seizures or barotrauma. As shown in Table 4, acute mucosal and skin reactions were modest and acceptable. Of all 45 patients in the study, 14 experienced a total of 25 severe late normal tissue complications. These are detailed in Table 5. Three patients underwent laryngectomy for complications and were noted to have no pathological evidence of disease in the laryngectomy specimen. Of interest, some of the patients with complications of necrosis were subsequently treated in the hyperbaric unit (without radiation) for their complicatons. Notably, all the severe complications became manifest within 2 years of treatment. The actuarial probability of freedom from severe complications was 58% at both 5 and 10 years (Fig. 2).

Tumor response

Of the 45 patients, 39 (87%) had a complete clinical response. Although routine biopsies were not performed in the post-treatment follow-up period, 9 of these 39 patients

Table 5. Larynx/HBO patients: severe chronic complications

Study ID#	Complications	Time to severe complications
1384	SF(GIV), FIST	3 mos
1435	SF(GIII), NEC, FIST, CAR BL	9 mos
1536	NEC	4 mos
1522	NEC	4 mos
1539	SF(GIII), FIST	7 mos
1817	SF(GIV), NEC, FIST	2 years
1875	NEC	3 mos
1935	NEC, FIST	5 mos
1987	SF(GIV)	8 mos
1998	NEC	8 mos
2121	NEC	1 year
2414	NEC, FIST	8 mos
2520	NEC	1 year, 6 mos
9991	SF(GIII), FIST	6 mos

SF = severe fibrosis; NEC = necrosis; FIST = fistula; CAR BL = carotid bleed.

underwent post-treatment biopsies and had pathological confirmation of complete response. As of February 1998, the overall survival for the 45 patients was 27% at 5 and 10 years. Including the non- and partial responders as local relapses, there were a total of 16 local failures resulting in an actuarial local recurrence-free survival of the entire patient cohort of 58% at 5 and 10 years. Limiting the analysis to the 39 patients who had a complete clinical response to therapy, the local recurrence-free survival was 69% at 5 and 10 years, respectively. The 5- and 10-year voice preservation rate for all 45 patients in the study was 46% and limiting the analysis to complete responders, the voice preservation rate at 5 and 10 years was 55% (Fig. 3). The voice preservation rate is lower than the local control rate due to the fact that three patients underwent laryngectomy for complications, but were locally controlled with no tumor in the laryngectomy specimen. There were a total of 16 regional relapses. Eleven of the 16 regional relapses were outside of the radiation fields. As noted previously, the field sizes employed were relatively small compared to current standards for patients with advanced laryngeal carcinoma.

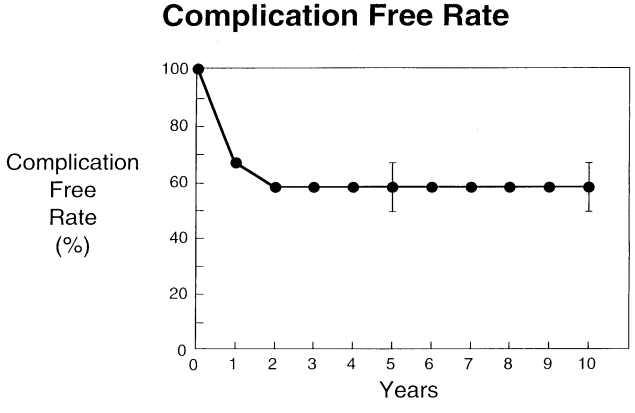

Fig. 2. Complication-free rate.

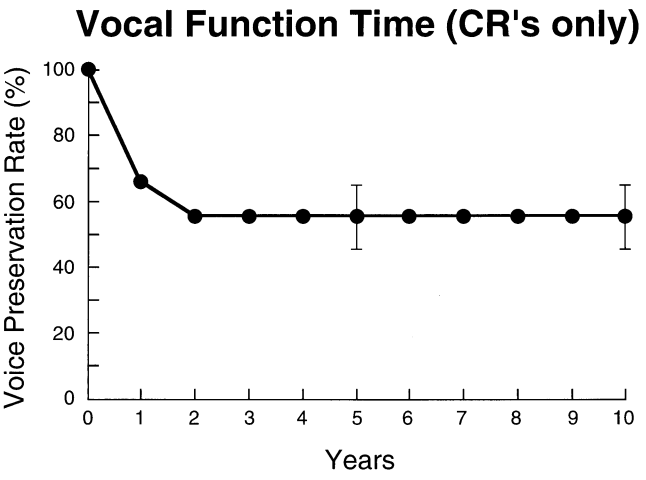

Fig. 3. Voice preservation rate.

The out-of-field regional failures, scored as marginal relapses, resulted in a relatively high 5-year marginal relapse rate of 30%, as shown in Fig. 4.

Overall results and prognostic factors

Overall patient outcome and actuarial statistics are summarized in Tables 6 and 7. Because all patients in the study were treated in similar fashion, there was no evidence of dose response. No significant association was found when local control or treatment complications were analyzed as a function of field size, hemoglobin level, stage or patient age. It should be noted, however, that the number of patients in the series limits interpretation of this analysis of complications and local control as a function of these parameters. Overall survival, as shown in Figs. 5 and 6, significantly correlated with patient age and stage of disease, with patients older than age 70 and those with more advanced stage faring poorly.

DISCUSSION

The existence within tumors of relatively radioresistant hypoxic cells has long been implicated as one of the con-

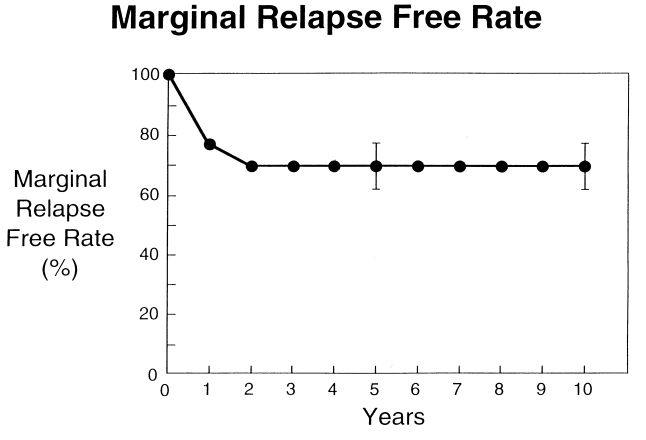

Fig. 4. Marginal (out of radiation field) relapse-free rate.

Table 6. Larynx patients outcome ($n = 45$)

	n	%
Response		
Complete	39	86.7
Partial	6	13.3
Local (LARYNX) relapse (complete responders only)	10	25.6
Regional relapses (includes marginal)	16	35.6
Marginal relapse (outside tx field)	11	24.4
Distant relapse	3	6.7
2nd primary	6	13.3
Functional voice	26	57.7
Final status		
Alive, NED	3	6.7
Dead, NED	25	55.5
Dead, WD	17	37.8

tributing factors to radiation failures (3–14). Although protracted fractionation schemes may minimize the hypoxic cell problem (6,24–32) a recent metaanalysis of hypoxic cell modification trials using either hypoxic cell sensitizers or hyperbaric oxygen demonstrated a highly significant benefit from these interventions in both local control and survival (11). A subset analysis of the trials clearly demonstrated that the majority of the benefit was noted in patients with squamous cell carcinoma of the head and neck. Several randomized trials evaluating hyperbaric oxygen in squamous cell carcinoma of the head and neck showed significant therapeutic gains with hyperbaric treatment. In the British MRC trial published by Henk *et al.* (6,7), which randomized 294 patients to 35 Gy in 10 fractions in air vs 35 Gy in 10 fractions in hyperbaric oxygen, no difference in overall survival was noted, but a highly significant benefit in local control was achieved in the hyperbaric arm. A subsequent trial from the MRC comparing the same hyperbaric regimen of 35 Gy in 10 fractions to conventional fractionation of 60 Gy in 30 fractions in air also demonstrated improved local control and survival in the hyperbaric arm (6,7). The Leeds trial reported by Berry *et al.* (2), which randomized only 24 patients with squamous cell carcinoma of the head and neck to treatment in air or treatment in hyperbaric oxygen, demonstrated statistically significant gains in both local control and survival. A randomized trial from South Africa evaluating 124 patients with head and neck cancer demonstrated a trend toward improved local

Table 7. Actuarial statistics

	5-Year	10-Year
Survival	27% ± 6	27% ± 6
Local relapse-free rate (all patients)	58% ± 8	58% ± 8
Local relapse-free rate (CRs only)	69% ± 8	69% ± 8
Marginal relapse-free rate	70% ± 8	70% ± 8
Voice preservation rate (CRs only)	55% ± 9	55% ± 9
Severe complication-free rate	58% ± 9	58% ± 9

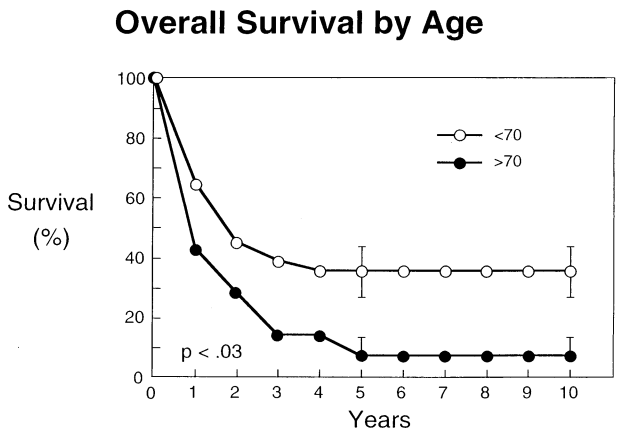

Fig. 5. Overall survival by patient age.

control with hyperbaric treatment (14). A trial from the Latter Day Saints reported by Sause *et al.*, however, which randomized 39 patients with head and neck cancer to 40 Gy in 12 fractions with hyperbaric oxygen vs 62.50 Gy in 25 fractions in air, failed to show a benefit to hyperbaric therapy (13). While there remain conflicting reports and controversies, the weight of the evidence clearly demonstrates potential therapeutic gains with the use of hyperbaric oxygen (11). However, the logistics of delivering radiation therapy with concomitant hyperbaric therapy are prohibitive with respect to conventional daily protracted radiation and all hyperbaric regimens involve hypofractionation to a greater or lesser extent.

The Peter MacCallum Cancer Institute schedule is an extreme example of this compromise: to facilitate treatment at a pressure of 4 atmospheres, patients had to be anesthetized and the radiotherapy was given in two large dose fractions of 10.5 to 11.5 Gy with a 21 day separation. Although acute skin and mucosal reactions using this regimen were modest and quite acceptable, severe late complications were significant with an actuarial probability of severe complications by 5 years of over 40%. With our current knowledge of the fractionation dependence of acute

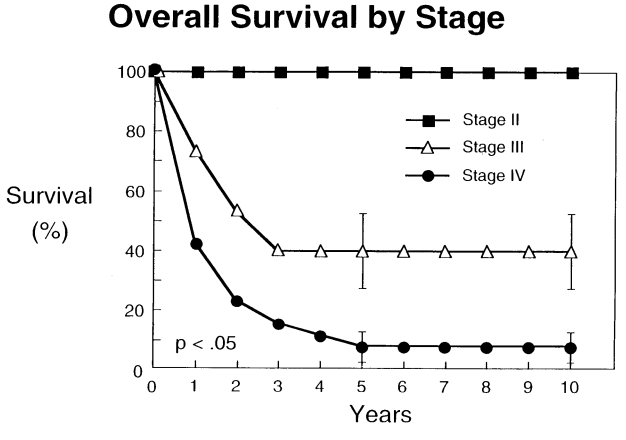

Fig. 6. Overall survival by stage.

Table 8. Advanced carcinoma of the larynx treated with radiation therapy (selected series)

Institution (Author)	Treatment program	# Patients	Patient selection	Voice preservation	Survival
VALSG (Wolf [34])	Induction chemotherapy radiation 70 Gy/35 fxs/7 wks	166	Stage III/IV glottic/supraglottic	64%	69% (2 years)
PMH (Harwood *et al.* [27])	Radiation alone 50 Gy/20 fxs/5 wks	89 T3N0 55 T4N0	Stage III/IV glottic	45–55%	34% (10years)
U. Florida (Mendenhall *et al.* [29])	Radiation alone 70 Gy/35 fxs/7 wks 74.40 Gy/62 fxs/6 wks	53	T3N0-3 glottic	64%	59% (5 years)
Michigan (Eisbruch *et al.* [23])	Induction chemotherapy accelerated RT 70.4 Gy/48 fxs/5.5 wks	33	Stage III/IV glottic/supraglottic	48%	70% (3 years)
Amsterdam (Croll *et al.* [19])	Radiation therapy alone 70 Gy/35 fxs/7 wks 67.5 Gy/54 fxs/6 wks	58	Stage III/IV glottic/supraglottic	67%	73% (5 years)
Peter MacCallum (Haffty)	Radiation therapy with hyperbaric oxygen-4 atmospheres 22 Gy/2 fxs/21 days	45	Stage III/IV glottic/supraglottic	46% (all pts) 55% (CRs)	27% (10years)

and late radiation reactions, this dichotomy between the severity of acute and late reactions is readily understandable (25,26,29). However, the question then arises as to whether a similar incidence of complications would have occurred if the patients had been treated in air (because of hypofractionation) or whether the hyperbaric oxygen per se contributed to the normal tissue injury. One can use the concept of biologically effective dose (BED) to compare the relative effects of different fractionation schedules on tissues with a given a/b ratio (25). Taking a representative a/b ratio of 3 for the types of complications seen in this patient cohort, the BED for the regimen of 23 Gy in 2 fractions is 111.2 Gy_3, a value not dissimilar from that of 70 Gy in 35 fractions (116.2 Gy_3). One may therefore conclude that at least some contribution to the development of late effects came from the hyperbaric oxygen itself. Both van den Brenk and Henk (6,7,15), in analyzing normal tissue reactions under hyperbaric conditions, noted enhancement of late reactions. Specifically, Henk reported a higher rate of laryngeal necrosis with hyperbaric treatment resulting in his recommending a 10% dose reduction when the larynx was included in the radiation field. On morphologic grounds, it is reasonable to posit that chondrocytes might exist in a state of relative hypoxia which could account for this observation. In addition, one would predict that the amount of sensitization in the PMCI series treated at 4 ATA would be greater than that in Henk's series treated at 3 ATA. Besides cartilage, there is evidence to suggest that oxygen tension at the time of radiotherapy is important in determining the risk of spinal cord injury (32). Fortunately (in retrospect), the treatment fields used for treatment of the patients in our series did not include the cord.

Radiosensitization of the laryngeal cartilage by hyperbaric oxygen would also explain the higher complication rate observed in this series than in the previous report of head and neck cases treated in a similar fashion at PMCI (17). Although follow-up was of a much shorter duration for the earlier report than for the present series, this cannot explain the discrepancy, since all the severe complications had their onset, somewhat surprisingly, within 2 years of treatment.

In terms of disease response and control, the results achieved were quite impressive. Forty of the 45 patients in the series had T3 or T4 primaries for which the standard surgical option would have been total laryngectomy. Nonetheless, a complete response was achieved in 39 patients of whom a functional voice was maintained in 26 (with an actuarial rate of larynx preservation of 55% in the complete responders), even though there were three laryngectomies for complications. The proportion of patients retaining a functional larynx is not significantly different from that achieved with induction chemotherapy in the VA trial and other contemporary series using conventional fractionation or accelerated fractionation with or without cytotoxic chemotherapy as shown in Table 8 (19,23,24,27,28,30,33–36).

The tumor BED for 23 Gy in two fractions is only 49.5 Gy_{10} compared with 84 Gy_{10} for a conventional course of 70 Gy in 35 fractions. The fact that similar tumor control rates were achieved is strong circumstantial evidence that hypoxic cells do limit the radiocurability of laryngeal cancer and that such cells can be effectively sensitized by hyperbaric oxygen. This has obvious implications for the use of hypoxic sensitizing agents such as the nitroimidizoles or drugs which target hypoxic cells such as mitomycin C or tirapazamine (1,4,5,8–12). Therapeutic strategies directed at the hypoxic cell problem using conventional or altered fractionation schedules, with the use of hypoxic cell cytotoxins, hypoxic cell sensitizers, or hyperbaric therapy are likely contribute to local control and result in an enhanced therapeutic ratio.

In summary, the historical experience at PMCI of hypofractionated radiotherapy in oxygen at 4 ATA has yielded important insights into the clinical radiobiology of advanced laryngeal cancer, although the treatment itself resulted in a less than optimal therapeutic ratio. It is important that historical data such as these are not lost or ignored.

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