

## Radiotherapy with fraction size of 2.25 Gy in T1-2 laryngeal and hypopharyngeal cancer

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This study was carried out to evaluate the influence of fraction size 2.25 Gy on local control of T1 and T2 laryngeal and hypopharyngeal cancers. Between August 2002 and December 2010, 80 patients with T1 and T2 laryngeal or hypopharyngeal cancers were treated with definitive radiotherapy with a fraction size of 2.25 Gy. Primary sites were the larynx in 69 and the hypopharynx in 11. Fifty-three patients were T1 and 27 were T2. All patients' pathology was squamous cell carcinoma except one carcinosarcoma. Radiotherapy was delivered 5 days/week with a 4-MV photon beam up to a total dose of 63.0 Gy. Median treatment time was 41 days. Statistical analysis of survival was calculated using the Kaplan–Meier method. No acute toxicity greater than grade 2 (CTCAE ver. 3.0.) including mucositis and dermatitis was observed. All but one patient had a complete response. The partial response patient received salvage surgery. The median follow-up period was 47 months (ranging from 4 to 108 months). No late toxicity greater than 1 was observed. Nine patients developed recurrence, seven local and two neck lymph nodes. Three patients died, one from laryngeal cancer and two from intercurrent diseases. The 5-year local control rates (LCRs) in the entire group, larynx T1, larynx T2 and hypopharynx T1 were 85.8%, 97.6%, 70.1% and 85.7%, respectively. The LCRs of T1 improved compared with our historical control, but not those of T2. The 2.25-Gy fraction size is safe and may have the potential to achieve good LCR in T1 lesions.

**Keywords:** hypofractionated radiotherapy; laryngeal cancer; hypopharyngeal cancer

### INTRODUCTION

Early stage laryngeal and hypopharyngeal cancers are good candidates for definitive radiotherapy. The five-year local control rates have been reported to be 85–94% in T1 larynx, 69–80% in T2 larynx [1], and 34–74% in T1 hypopharynx [2, 3]. However, these treatment results are not satisfactory, and some attempts have been made to improve local control. The strategies are higher total dose, hyperfractionated radiotherapy, concurrent

chemotherapy and hypofractionated radiotherapy. In early glottic cancer, some reports suggested that a fraction dose higher than 2 Gy could lead to better local control than a lower fraction dose [4, 5]. Higher fraction doses need better dose distribution to avoid normal tissue toxicity such as acute mucositis, dermatitis, late laryngeal edema and cartilage necrosis. Parallel opposed wedged fields could not always create homogeneous dose distribution, and a more precise radiation technique would improve dose homogeneity.

Treatment modification with hyperfractionation or concurrent chemotherapy tends to be standard for advanced laryngeal and pharyngeal tumors [1–3], but those modalities have the burden of greater treatment cost and time, and they are not supported by enough evidence in early-stage tumors of improved local control and survival. In our institute, we focused on hypofractionated radiotherapy, which is a modality without additional burden to the patients. We therefore conducted a clinical study to evaluate the effect of a fraction size of 2.25 Gy on local control of T1 and T2 laryngeal and hypopharyngeal cancers.

## MATERIALS AND METHODS

### Eligibility

Patients were eligible for this study if they met the following entry criteria: histologically proven malignant tumor of the larynx or hypopharynx; T1N0M0 or T2N0M0 tumor according to the International Union Against Cancer (UICC) criteria 2002 or T1-2N1-2M0 in status post radical neck dissection; no previous treatment to the primary tumor; and performance status by Eastern Cooperative Oncology Group (ECOG) criteria of  $\geq 1$ . Patients were excluded if they had other active untreatable cancers, any active collagen disease or a history of radiotherapy in the tumor region. Evaluation before treatment consisted of medical histories, physical examination, endoscopic examination of the laryngopharynx, magnetic resonance imaging (MRI) of the neck, computed tomography (CT) of the neck, chest and abdomen, and endoscopic examination of the upper digestive tracts. Written informed consent on treatment methods, expected results and potential adverse effects was obtained before treatment.

### Radiotherapy

Radiotherapy for all the patients was planned using the Eclipse three-dimensional treatment planning system (Varian Medical Systems, Palo Alto, CA, USA). To facilitate treatment planning, CT of the neck was obtained with each patient in the supine position with thermoplastic immobilization shell. The clinical target volume (CTV) was defined as the entire tumor invasion subsite. The planning target volume (PTV) was obtained by adding a 10-mm margin to the CTV and an additional 15-mm margin from the skin. No prophylactic neck lymph node area irradiation was performed. In T1 glottic tumor, the field size is approximately 6 × 6 cm in lateral view. Radiation fields were customized as appropriate by a multileaf collimator. Electronic tissue compensation planning was performed using the Eclipse software to ensure uniform dose distribution and to achieve target dose homogeneity within  $\pm 7\%$  of PTV. All sites were irradiated with 4-MV photon beams (Clinac 21EX; Varian), parallel opposed fields. The daily

dose was 2.25 Gy per fraction up to a total dose of 63.0 Gy in 28 fractions.

### Evaluation

All patients underwent serial clinical examinations to evaluate their tumor response and acute toxic reactions. Treatment response was assessed at 1 month after treatment completion by physical examination, CT or MRI of the neck. Complete response (CR) was defined as complete clinical, physical and radiological disappearance of the tumor. Partial response (PR) was defined as a minimum 50% reduction in the product of the longest perpendicular diameter of the most easily measurable or largest tumor mass within the irradiation field. Stable disease (SD) was characterized as a reduction of  $< 50\%$  or a progression of  $< 25\%$ . Progressive disease (PD) was characterized as a progression of  $> 25\%$ . Local control was defined as tumor control within the field of radiation.

Acute toxicities were assessed weekly and graded according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE ver. 3.0). Late treatment-related toxicities were graded according to the Radiation Therapy Oncology Group/European Organization of Research and Treatment of Cancer's Late Effect Normal Tissue (LENT/SOMA) scores.

Statistical analyses of local control (LC) rate and survival rate were performed using the Kaplan–Meier method. Local control was defined as tumor control within radiation field. Relapse free (RF) was defined as tumor control in the whole body, within and outside of radiation field. Cause specific survival (CSS) was defined as survival calculated by laryngeal or hypopharyngeal cancer deaths, excluding death from other causes.

## RESULTS

### Patients

Between August 2002 and December 2010, 80 patients with T1 and T2 laryngeal or hypopharyngeal cancers were treated with this regimen (Table 1). Their ages ranged from 47 to 83 years, with a median of 63 years, and 75 (90%) patients were male. Primary sites were the larynx in 69 and hypopharynx in 11. There were 3 cases of supraglottic tumor, 64 of glottic tumor and 2 cases of subglottic tumor. All patients had squamous cell carcinoma except one carcinosarcoma. Fifty-three patients were T1 and 27 patients were T2. Fifty-three of the patients were stage I, 25 were stage II and 2 were stage IVA and had undergone radical neck dissection. The relations between T and N classification and primary site are shown in Table 2. There were 3 cases of synchronous cancer (esophagus and hepatocellular carcinoma 1, esophagus 1, skin 1), and 10 cases had a history of metachronous cancer (esophagus 2, stomach 3, lung and esophagus 1, colon 1, stomach and bladder 1,

**Table 1.** Patients and tumor characteristics

No. of cases	80	(%)
Age (years; median)	47–83 (63)	
Gender		
Male	75	(93.8)
Female	5	(6.3)
Primary site		
Larynx <sup>a</sup>	69	(86.3)
Hypopharynx	11	(13.8)
Pathology		
Squamous cell	79	(98.8)
Carcinosarcoma	1	(1.3)
T stage		
T1	53	(66.3)
T2	27	(33.8)
N stage		
N0	78	(97.5)
N2 (after radical neck)	2	(2.5)
Stage		
I	53	(66.3)
II	25	(31.3)
IVA	2	(2.5)

<sup>a</sup>Glottic 64, Supraglottic 3, Subglottic 2.

**Table 2.** T and N stage classification

T N classification	Larynx	Hypopharynx	Total
T1N0	42 <sup>a</sup>	10	52
T1N2	0	1	1
T2N0	26 <sup>b</sup>	0	26
T2N2	1	0	1
Total	69	11	80

<sup>a</sup>Supraglottic 2, <sup>b</sup>Supraglottic 1, Subglottic 2.

In N2 case, radical neck dissection was performed before radiotherapy.

breast 1, bladder 1). The patients have synchronous double primary, all other primaries were treated in radical intent.

### Compliance with treatment

Definitive radiotherapy of 63 Gy was completed in all patients. The overall treatment time ranged from 38 to 49 days, with a median of 41 days. The most common acute toxicity was mucositis. Mucositis and dermatitis of grade 2

**Table 3.** Acute adverse effects

Grade	0	1	2	3	4
Mucositis	0	3	77	0	0
Dermatitis	0	65	15	0	0

CTCAE version 3.0.

were observed in 77 cases (96%) and 15 cases (19%), respectively. No grade 3 acute toxicity was observed (Table 3).

### Treatment response

One case of T2 glottic could not reach CR, but all other cases reached CR. The PR case underwent total laryngectomy 8 months after the completion of radiotherapy. The median follow-up period was 47 months (ranging from 4 to 108 months). Nine patients developed recurrence, seven local and two neck lymph nodes. In the seven local recurrent cases, five were T2 glottic, one T1 glottic and one T1 hypopharynx. Both neck lymph node recurrent cases had T2 glottic tumor. As for salvage treatment, six glottic cancer patients with local recurrence underwent laryngectomy, one hypopharynx patient with local recurrent tumor received endoscopic mucosal resection and two neck lymph node recurrent patients had radical neck dissection. The PR cases, four patients with primary recurrence, and two patients with neck lymph node recurrence were successfully salvaged by surgery. Two patients had recurrence systemically after surgery and received chemotherapy. However, they were not salvaged successfully.

### Late toxicities

Two patients had grade 1 laryngeal edema. No other severe late toxicities were observed.

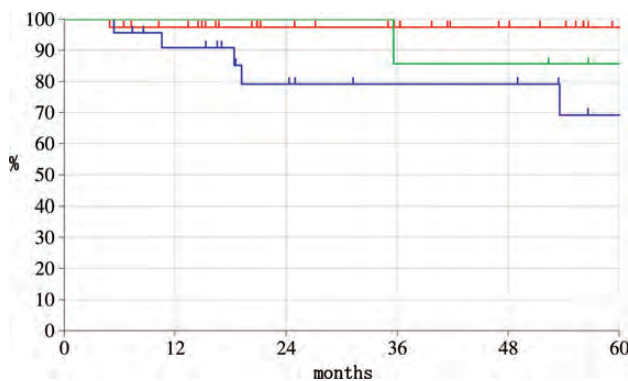
### Survival

One patient has been living with systemic recurrent disease and one patient died of laryngeal cancer. Four patients developed second malignancies after the treatment of laryngeal or hypopharyngeal cancer, two in the esophagus, one in the prostate and one in the lung and pancreas. One patient died of pancreatic cancer and one patient died of renal failure.

The 5-year LC rates, RF rates and CSS rates are shown in Table 4. The 5-year LC rates in the entire group, all T1, larynx T1, hypopharynx T1 and larynx T2 were 85.8%, 94.7%, 97.6%, 85.7% and 70.1%, respectively. The 5-year LC rates of glottic T1, glottic T2 and hypopharynx T1 squamous cell carcinoma were 97.4%, 67.3% and 85.7%, respectively (Fig. 1). The 5-year LC rates of glottic T1 and glottic T2 squamous cell carcinoma cases were 97.4% (95% confident interval 92.3–100) and 69.2% (95% IC

**Table 4.** Five-year local control (LC), relapse free (RF) and cause specific survival (CSS) rates (%) with 95% confidence interval

Group (No. of cases)	LC (95% IC)	RF (95% IC)	CSS (95% IC)
All (80)	85.8 (76–95.6)	83.7 (73.2–94.4)	96.3 (91.2–100) (%)
T1 (53)	94.7 (87.3–100)	94.7 (87.3–100)	100 (100)
T2 (27)	70.1 (48.1–92.1)	64.4 (41.1–87.7)	90.0 (83.3–96.7)
Larynx T1 (42)	97.6 (92.9–100)	97.6 (92.9–100)	100 (100)
Larynx T2 (27)	70.1 (48.1–92.1)	64.2 (41.1–87.7)	90.0 (83.3–96.7)
Hypopharynx T1 (11)	85.7 (59.8–100)	85.7 (59.8–100)	100 (100)

**Fig. 1.** Local control rates by T stage and site. The 5-year LC rates of glottic T1, glottic T2 and hypopharynx T1 squamous cell carcinoma were 97.4%, 69.3% and 85.7%, respectively.

44.4–90.2), respectively (excluding one carcinosarcoma case).

The significant prognostic factor in the 5-year LC rates was the T stage. The 5-year RF rates in the total group, all T1, larynx T1, hypopharynx T1 and larynx T2 were 83.8%, 94.7%, 97.6%, 85.7% and 64.4%, respectively. The significant prognostic factor in the 5-year RF rates was T stage ( $P < 0.05$ ). The 5-year CSS rates in the total group, T1, and T2 were 96.3%, 100% and 94.3%, respectively.

## DISCUSSION

There are multiple treatment options for early-stage laryngeal and hypopharyngeal cancer [1–3]. In these early stage tumors, local control with organ preservation is the first priority. Treatment options include laser excision, endoscopic submucosal resection, partial laryngo-pharyngectomy, total laryngo-pharyngectomy and definitive radiotherapy (RT). Treatment selection is based on the tumor extension, physician's recommendation and patient's preference. Small-sized T1a tumors of the glottis could be a good candidate for laser excision, and small-sized superficial hypopharyngeal T1 tumors could be successfully treated by endoscopic

submucosal resection. However, tumors not controllable with such a light burden treatment or with the treatment affecting voice quality make good candidates for RT.

There are some factors that modify the laryngeal tumor control probability of RT. Involvement of anterior commissure, beam energy, field size, daily fraction dose, total dose, overall treatment time, male gender and pre-treatment hemoglobin level have been reported [1–3]. To improve tumor control, total dose increase by hyperfractionated radiotherapy, shorter treatment time by accelerated radiotherapy and radiation enhancement by concurrent chemotherapy have been conducted, but these protocols could not improve T1 tumor control significantly without increasing adverse effects. The DAHNAKA trial of 6 days/week treatment protocol that completes treatment in 39 days improved outcome compared with the conventional 5 days/week treatment protocol that takes 46 days [6]. However, it had been not used widely in clinical practice because of the inconvenience of the necessary weekend hospital visit. In such situations, several studies have reported that a daily fractionation dose higher than 2 Gy improved local control. Shorted treatment time may improve the patient's quality of life unless it increases acute adverse effects.

In this study, we focused on the daily fraction dose and conducted clinical trials from 2002 to 2010. Table 5 shows previously reported hypofractionated RT for early glottic tumors [5, 7–11]. For T1 glottic tumor control, Mendenhall *et al.* reported a 5-year LC rate of 100% with a 2.25-Gy daily fraction, superior to the 80% from that with 2 Gy [7]. Le *et al.* reported a glottic cancer local control rates of 79% with a daily fraction < 1.8 Gy, 94% > 2.25 Gy in T1, 44% in daily fraction < 1.8 Gy, 100% > 2.25 Gy in T2, total dose, fraction dose, overall treatment time were the significant prognostic factors in multivariate analysis [5]. Cellai *et al.* reported 5-year LC rates of 85% with a daily fraction < 2 Gy, 83% in 2.1–2.4 Gy and 84% with > 2.25 Gy for T1 tumors [8]. Frata *et al.* reported 5-year LC rates of 69% with a daily fraction < 2 Gy, 78% with 2.1–2.4 Gy and 71% with > 2.25 Gy for T2 tumors [9]. Yamazaki *et al.* reported a 5-year LC rate of 92% with a 2.25-Gy daily fraction, which was better than 77% from that with 2 Gy [10].

**Table 5.** Five-year local control rates for T1N0 and T2N0 glottic squamous cell carcinoma

First author	Daily dose (Gy)	No. of cases	T1		T2	
			No. of cases	5yLC (%)	No. of cases	5yLC (%)
Mendenhall [7] 1988	2.25			100		
	2–2.2			80		
Le [5] 1997	<1.8	122		79	24	44
	1.8–1.99	93		92	35	79
	2.0–2.24	46		81	13	73
	≥2.25	51		94	11	100
Cellia [8] 2005 Franta [9] 2005	≤2	503		85	142	69
	2.1–2.4	312		83	104	78
	>2.4	16		84	10	71
Yamazaki [10] 2006	2	89		77		
	2.25	91		92		
Gultekin [11] 2011	2.3	183		81		
Present study	2.25	39		98	24	69

Gultekin *et al.* reported a 5-year LC rate of 81% in a 2.3-Gy daily fraction [11].

In the present study, eight cases were T2 and one was T1 in nine recurrent or PR glottis cases. Both cervical recurrent cases were T2 and both non-salvaged cases were T2. The 5-year LC rates of glottic T1 and glottic T2 squamous cell carcinoma cases were 97.4% and 69.2%, respectively.

In our previous experiences, 5-year LC of T1 squamous cell laryngeal carcinoma was 85% ( $n=82$ ), and T2 was 79% ( $n=40$ ) with 1.8–2.0 Gy/fraction [12]. In 1993, we reported the results of a clinical trial of hyperfractionated radiotherapy with 1.5 Gy/fraction twice a day up to 72 Gy in 48 fractions. Forty-two cases of T2N0M0 squamous cell glottic carcinoma were registered and 5-year LC was 75.6%, not superior to the 55 cases of historical control of 73.2% [13]. The current LCR of 97.4% of T1 tumor with 2.25 Gy/fraction is better than our previous experience, although the LCR of 67.3% of T2 tumor with 2.25 Gy/fraction is lower in than our previous studies.

Concerning early-stage hypopharyngeal cancer, the treatment result was not satisfactory. Concurrent chemotherapy and hyperfractionated radiotherapy have been conducted to improve LC. Reports of hypopharyngeal T1 tumor control have varied. Nakamura *et al.* reported 115 cases of stage I–II from 10 institutes, 5-year overall survival (OS), CSS in patients without synchronous cancer were 66.0%, 77.4%, and LC of T1 was 76.5% [14]. Fractionation and total doses varied in their study. Nakajima *et al.* reported the treatment results of 103 cases of T1–T2 hypopharyngeal tumors treated with 2 Gy/fraction. Three-year OS, CSS for T1–T2 were 70%, 79% and LC for T1 was 87% [15]. Yoshimura *et al.* reported the analysis of 77 cases with T1–T2 hypopharyngeal cancer treated with 2 Gy/fraction, 5-year OS, CSS, recurrence-free survival rates were 47%,

74% and 57% in all cases, and 42%, 85% and 75% in T1 cases [16].

In the present study, 1 of 11 hypopharyngeal T1 cases recurred. This case had a history of early esophageal cancer and also recurrent esophagus multicentric metachronous cancer, treated with submucosal resection. The 5-year LC rate of hypopharynx T1 was 85.7%.

Overall treatment time was thought to be one of the keys for tumor control. But in our study, median treatment time in control patients and recurrent patients was the same at 41 days, with a range of 38 to 48 days in control and 38 to 49 days in recurrent patients. Two patients with prolonged treatment time had recurrence, with one local recurrent case being treated in 49 days and one cervical lymph node recurrent case in 47 days. The other eight patients with residual tumor or recurrence had been irradiated within the initially scheduled period.

If greater daily fraction dose increased adverse effects, we could not use a greater dose. But according to our data, no severe adverse effects have been observed. Mendenhall *et al.* reported that higher daily fraction doses resulted in higher LC rates without a significant increase in acute adverse effects [7]. Cellai *et al.* reported that higher fraction doses significantly increased the incidence of late adverse effects. However, we have not observed any increase in late adverse effects. Hypofractionation radiotherapy reduced the treatment time and cost. In terms of biologically effective dose (BED), 63 Gy in 28 fractions is equal to 66 Gy in 33 fractions. This may reduce the burden on both patients and institutes.

Our study has many limitations, mainly due to the fact that this was a phase II non-randomized trial in only 80 patients over a 9-year period. Moreover, some patients were lost to follow-up. In T1 laryngeal cancer, we could not

analyze other factors affecting LC due to the high LCR. In T2 tumor, tumor volume might be affected in LC, but we did not measure that in this study.

Despite these limitations, we propose that a 2.25-Gy daily fraction in T1 laryngeal and hypopharyngeal tumor may be a safe method and valuable in LC, even if adverse effects are at the same level as with standard fractionation. However, in T2 laryngeal tumor, LC showed no improvement compared with the historical control, therefore, more effective treatment strategies including dose escalation will be necessary.

## REFERENCES

- Mendenhall WM, Hinerman RW, Amder RJ *et al.* Larynx. In: Halperin EC, Perez AC, Brady LW (eds). *Perez and Brady's Principles and Practice of radiation Oncology* (5th ed). Philadelphia: Lippincott Williams & Wilkins, 2008, 975–95.
- Shah HK, Khuntia D, Hoffman HT *et al.* Hypopharynx cancer. In: Halperin EC, Perez AC, Brady LW (eds). *Perez and Brady's Principles and Practice of radiation Oncology* (5th ed). Philadelphia: Lippincott Williams & Wilkins, 2008, 958–74.
- Garden AS, Morrison WH, Ang KK. Larynx and hypopharynx cancer. In: *Clinical Radiation Oncology* (2nd ed.). Churchill Livingstone: Elsevier, 2007, 727–53.
- Fein DA, Lee WR, Hanlon AL *et al.* Do overall treatment time, field size, and treatment energy influence local control of T1–T2 squamous cell carcinomas of the glottic larynx? *Int J Radiat Oncol Biol Phys* 1996;**34**:823–31.
- Le QT, Fu KK, Kroll S. Influence of fraction size, total dose, and overall time on local control of T1–T2 glottic carcinoma. *Int J Radiat Oncol Biol Phys* 1997;**39**:115–26.
- Overgaard J, Hansen HS, Specht L *et al.* Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck DAHANCA 6 and 7 randomised controlled trial. *Lancet* 2003;**20**:933–40.
- Mendenhall WM, Parsons JT, Million RR *et al.* T1-2 squamous cell carcinoma at the glottic larynx treated with radiation therapy. Relationship of dose fraction factors to local control and complications. *Int J Radiat Oncol Biol Phys* 1988;**5**:1267–73.
- Cellai E, Frata P, Margrini SM *et al.* Radical radiotherapy for early glottic cancer: results in a series of 1087 patients from two Italian radiation oncology centers I. The case of T1N0 disease. *Int J Radiat Oncol Biol Phys* 2005;**63**:1378–86.
- Frata P, Cellai E, Magrini SM *et al.* Radical radiotherapy for early glottic cancer: results in a series of 1987 patients from two Italian radiation oncology centers. II. The case of T2N0 disease. *Int J Radiat Oncol Biol Phys* 2005;**63**:1387–94.
- Yamazaki H, Nishiyama K, Tanaka E *et al.* Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. *Int J Radiat Oncol Biol Phys* 2006;**64**:77–82.
- Gultekin M, Ozyar E, Cengiz M *et al.* High daily fraction dose external radiotherapy for T1 glottic carcinoma: Treatment results and prognostic factors. *Head Neck* 2012; **34**:1009–14.
- Karasawa K, Okawa T, Kita-Okawa M *et al.* Radiotherapy for early (T1–T2) glottic cancer: experience of Tokyo Women's Medical College (1966–1986). *International Congress of Radiation Oncology'93 abstracts*, 250, 1993.
- Karasawa K. Clinical investigation of twice-a-day fractionation radiotherapy for glottic cancer. *J Tokyo Women's Medical College* 1993;**63**:1500–9.
- Nakamura K, Shioyama Y, Kawashima M *et al.* Multi-institutional analysis of early squamous cell carcinoma of the hypopharynx treated with radical radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;**65**:1045–50.
- Nakajima A, Nishiyama K, Morimoto M *et al.* Definitive radiotherapy for T1-2 hypopharyngeal cancer: a single-institution experience. *Int J Radiat Oncol Biol Phys* 2012; **82**(2):e129–35.
- Yoshimura R, Kagami Y, Ito Y *et al.* Outcomes in patients with early-stage hypopharyngeal cancer treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 2010; **77**: 1017–1023.