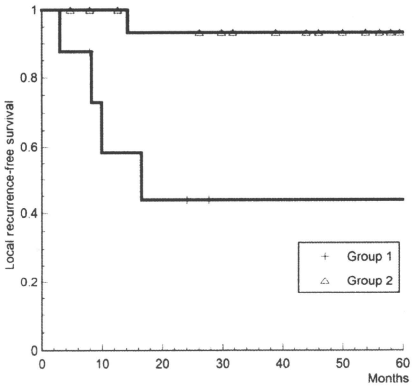

Fig. 3. Local recurrence-free survivals according to the group classification by surgical margin status and number of previous operations (for details refer to the text).

(Fig. 3). The difference reached a statistical significance with $p = 0.004$. Sex, malignant grade, tumor size, number of applicators, and treated volume were found to have no statistically significant influences on LRFS. In the 23 lesions of the extremity STSs, only one amputation was required to control recurrence.

OS of 25 patients was 75.6% in 5 years. There were only 2 patients with Grade 1 malignancy and both of them were alive without recurrence. The patients with Grade 2 and 3 lesions showed similar OSs and 71.6% of them were alive for 5 years.

Acute morbidities were seen in 7 patients with Grade 1 morbidities in 6 patients and Grade 2 in 1 patient (Table 3). Grade 1 morbidities were a slight bleeding from the scar at the time of applicator removal, slight erosion of skin, and seroma formation requiring aspiration only once or twice. Grade 2 morbidity was wound dehiscence, which healed with conservative measures. Chronic morbidities were seen in 4 patients. The Grade 3 and 4 morbidity were seen each in 1 patient. Grade 4 morbidity was bone exposure at the HDRBT site requiring surgical removal of the sequester and repair with bone transplantation. The Grade 3 morbidity was fistula formation with an ensuing infection managed by debridement. Both morbidities occurred within 24 months after HDRBT. Five-year rate of chronic morbidities equal to or greater than Grade 2 was 14.6%.

Table 3
Number of morbidities of postoperative high–dose rate brachytherapy

Morbidities	Morbidity grade	Number of morbidities
Acute morbidity		
Wound complication	1	4
	2	2
Paresthesia	1	1
Seroma formation	1	1
Late morbidity		
Wound complication	2	1
Seroma formation	1	1
Bone exposure	4	1
Infectious fistula	3	1

Discussions

In the management of STS, limb-sparing operation with perioperative radiation therapy has been established as a standard (13). With that combination, LRFS rate is reported to be 75–100% (1–4, 14). However, local recurrence rate is strongly influenced by the surgical margin status, number of previous operations, grade of malignancy, and primary site of STS (1, 2). In the present study, operative margins were microscopically positive in 50% of the patients and the remaining patients had very close margins less than 5 mm. Furthermore, 54% of the lesions were classified as Grade 3 malignancies. Considering the adverse features of this series, LRFS rate of 78.2% in 5 years is relatively favorable. The marginal status, number of the previous operations, and the grade of malignancy did not have an influence on LRFS with a statistical significance, probably because of the small number of the patients in this series. However, the recurrent lesions resected with positive surgical margins showed a poor 5-year LRFS of 43.8% in comparison to the other lesions with 93.3% LRFS in 5 years.

Brachytherapy has an advantage of concentrating dose distribution onto the tumor region with a simultaneous sparing of normal tissues (15), whereas EBRT with wide fields encompassing tumor as well as surgical beds sometimes causes bone fracture, subcutaneous fibrosis, and lymphedema distal to the irradiated site (16). According to Memorial Sloan-Kettering Cancer Center studies, postoperative LDRBT as a single modality reduces local recurrence in margin-negative high-grade STS (1, 3). The LDRBT did not include operative scars and drainage scars in the treated volume. In contrary, local recurrence was not reduced by LDRBT alone in postoperative low-grade STSs (17). They also suggested that high-grade STSs with positive surgical margins are better treated by combination of EBRT and LDRBT (5). Although HDRBT has advantages that radiation dose distribution can be optimized by the manipulation of dwell positions and dwell times of ^{192}Ir source, and radiation exposure to the medical personnel is negligible, the paucity of reported series makes it difficult to establish the optimal fractionation and total dose of HDRBT (6–10). Retrospective analyses revealed that combined EBRT and HDRBT is well tolerated and reduce local recurrence. Chun *et al.* (6) showed that local recurrence was not seen in 17 patients treated with 12–18 Gy

of 6 fractions of HDRBT combined with EBRT of 36–60 Gy. Pohar *et al.* (9) demonstrated that 2-year local control of 94% could be obtained with HDRBT of 13.5 Gy in three fractions with EBRT. Koizumi *et al.* (7) showed somehow poorer local control rate of 48% in 2 years because of the adverse features of their patients with macroscopic residual disease in 31%. In the present study, HDRBT was used without EBRT. HDRBT was delivered to the tumor bed without including surgical and drainage scars. At the launch of the postoperative HDRBT, radiation was planned to be confined to the tumor bed based on the reports from Memorial Sloan-Kettering Cancer Center. Because most of the patients in this series underwent resections reaching to the major neurovascular bundles and the high-dose radiation to them could cause serious morbidities, the total dose of HDRBT was determined by tolerance dose of peripheral nerve assumed as about 60 Gy in a conventional fractionation. The corresponding biologically equivalent dose by 2 Gy fractionation was calculated by linear quadratic model assuming $\alpha/\beta = 10$ Gy and 3 Gy for tumor control and late toxicity, including nerve damage, respectively (18). The equivalent dose by 2 Gy fractionation for HDRBT of 36 Gy was 48 Gy and 64.8 Gy, respectively, for tumor control and late toxicity. Because of the favorable results, this field setup and fractionation regimen of HDRBT have been continued to the present time.

Despite the retrospective nature of this study and the small number of patients, HDRBT alone with the fractionation regimens used in this study seems to be satisfactory to sterilize lesions in the treated volume. However, poor LRFS of 43.8% in 5 years demonstrates that in lesions treated for recurrence and whose surgical margins are positive, STSs tended to recur outside of the treated volume of HDRBT but within 5 cm from the surgical scars. It seems that they had better been treated with combination of HDRBT and wide field EBRT encompassing surgical beds as well as scars and drainage sites.

Serious late morbidity was seen in 2 patients, both of which could be repaired by surgical procedures. Although it is recommended to begin brachytherapy no sooner than 5 days after the operation (1, 15), 2 patients irradiated with a shorter interval did not have any serious morbidities. There were no patients who underwent limb amputation because of morbidities.

Conclusions

In summary, HDRBT alone to the tumor bed without including surgical scars and drainage sites with 36 Gy/6 fractions/3 d seems to be adequate and tolerable as a postoperative treatment for patients initially operated and/or negative for surgical margins. If the lesion is operated for recurrence and surgical margins are positive, administration of wide fields EBRT is recommended.

Acknowledgment

This work was partly supported by Grant-in-Aid for Cancer Research from the Ministry of Health, Labor, and Welfare, Japan.

References

[1] Pisters PWT, Leung DHY, Woodruff J, *et al.* Analysis of prognostic factors in 1041 patients with localized soft tissue sarcomas of the extremities. *J Clin Oncol* 1996;14:1679–1689.

[2] Zagars GK, Ballo MT, Pisters PWT, *et al.* Preoperative vs. postoperative radiation therapy for soft tissue sarcoma: A retrospective comparative evaluation of disease outcome. *Int J Radiat Oncol Biol Phys* 2003;56:482–488.

[3] Pisters PWT, Harrison LB, Leung DHY, *et al.* Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol* 1996;14:859–868.

[4] Yang JC, Chang AE, Baker AR, *et al.* Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol* 1998;16:197–203.

[5] Alekhteyar KM, Leung DH, Brennan MF, *et al.* The effect of combined external beam radiotherapy and brachytherapy on local control and wound complications in patients with high-grade soft tissue sarcomas of the extremity with positive microscopic margin. *Int J Radiat Oncol Biol Phys* 1996;36:321–324.

[6] Chun M, Kang S, Kim BS, *et al.* High dose rate interstitial brachytherapy in soft tissue sarcoma: Technical aspects and results. *Jpn J Clin Oncol* 2001;31:279–283.

[7] Koizumi M, Inoue T, Yamazaki H, *et al.* Perioperative fractionated high-dose rate brachytherapy for malignant bone and soft tissue tumors. *Int J Radiat Oncol Biol Phys* 1999;43:989–993.

[8] Martinez-Monge R, San Julian M, Amillo S, *et al.* Perioperative high-dose-rate brachytherapy in soft tissue sarcomas of the extremity and superficial trunk in adults: Initial results of a pilot study. *Brachytherapy* 2005;4:264–270.

[9] Pohar S, Haq R, Liu L, *et al.* Adjuvant high-dose-rate and low-dose-rate brachytherapy with external beam radiation in soft tissue sarcoma: A comparison of outcomes. *Brachytherapy* 2007;6:53–57.

[10] Nag S, Porter AT, Donath D. The role of high dose rate brachytherapy in the management of adult soft tissue sarcomas. In: Nag S, editor. *High dose rate brachytherapy. A textbook.* New York, NY: Futura Publishing Company; 1994. p. 393–408.

[11] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.

[12] Perez CA, Brady LW. Principles and practice of radiation oncology. Philadelphia, PA: JB Lipppincot Company; 1993. pp. 53–55.

[13] Pisters PWT, O'Sullivan B, Maki RG. Evidence-based recommendations for local therapy for soft tissue sarcomas. *J Clin Oncol* 2007;25:1003–1008.

[14] Suit HD, Mankin HJ, Wood WC, *et al.* Treatment of the patient with stage M0 soft tissue sarcoma. *J Clin Oncol* 1988;6:854–862.

[15] Nag S, Shasha D, Janjan N, *et al.*, American Brachytherapy Society. The American Brachytherapy Society recommendations for brachytherapy of soft tissue sarcomas. *Int J Radiat Oncol Biol Phys* 2001;49:1033–1043.

[16] Davis AM, O'Sullivan B, Turcotte R, *et al.*, Canadian Sarcoma GroupNCI Canada Clinical Trial Group Randomized Trial. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol* 2005;75:48–53.

[17] Pisters PWT, Harrison LB, Woodruff JM, *et al.* A prospective randomized trial of adjuvant brachytherapy in the management of low-grade soft tissue sarcomas of the extremity and superficial trunk. *J Clin Oncol* 1994;12:1150–1155.

[18] Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989;62:679–694.

Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 4, pp. 1017–1023, 2010

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.06.066

CLINICAL INVESTIGATION **Head and Neck**

OUTCOMES IN PATIENTS WITH EARLY-STAGE HYPOPHARYNGEAL CANCER TREATED WITH RADIOTHERAPY

RYO-ICHI YOSHIMURA, M.D.,*† YOSHIKAZU KAGAMI, M.D.,* YOSHINORI ITO, M.D.,* MASAO ASAI, M.D.,‡ HIROSHI MAYAHARA, M.D.,* MINAKO SUMI, M.D.,* AND JUN ITAMI, M.D.*

Division of *Radiation Oncology and ‡Head and Neck Surgery, National Cancer Center Hospital, and †Department of Diagnostic Radiology and Oncology, Head and Neck Reconstruction Division, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan

Purpose: To analyze the outcome in patients with early-stage hypopharyngeal cancer (HPC) who were treated with radiotherapy (RT).

Methods and Materials: Between February 1988 and February 2007, 77 patients with Stage I or Stage II HPC underwent definitive RT in the Division of Radiation Oncology at the National Cancer Center Hospital. Eleven of the patients received local irradiation, and the other 66 patients received elective bilateral neck irradiation and booster irradiation to the primary lesion. The median follow-up period for all the patients was 33 months from the start of RT, ranging from 3 to 229 months.

Results: The rates of overall survival, HPC-specific survival, HPC recurrence-free survival, and local control with laryngeal voice preservation for the 77 patients at 5 years were 47%, 74%, 57%, and 70%, respectively. The survival rates were not affected by the patient characteristics or treatment factors, but the RT field was significantly correlated with local control in a multivariate analysis. Seven of the patients had Grade 3 or greater complications, but these complications occurred after salvage surgery in 6 of the patients. Of the 77 patients, 83% had synchronous or metachronous malignancies, but these malignancies did not influence the survival of the patients if the malignancies were detected at an early stage.

Conclusion: RT is an appropriate treatment method for early-stage HPC. However, because synchronous or metachronous malignancies occur at a relatively high frequency, careful follow-up and the early detection of such malignancies are critical. © **2010 Elsevier Inc.**

Hypopharyngeal cancer, Radiotherapy, Synchronous malignancy, Metachronous malignancy.

INTRODUCTION

Patients with hypopharyngeal cancer (HPC) are often first diagnosed at an advanced stage. Because the diagnosis of early-stage HPC is relatively rare, few reports have analyzed the treatment results of early-stage HPC; thus, the optimal treatment for this condition remains uncertain (1).

Foote (2) reported that treatment options for early-stage HPC included endoscopic removal, open function-sparing partial laryngopharyngectomy, total laryngectomy with partial pharyngectomy, and radiotherapy (RT); factors in treatment selection were reported to be the extent and volume of the tumor (including anterior commissure involvement), patient preference (including occupational considerations), patient age, comorbid illnesses, patient compliance, voice quality, physician experience and skill, previous head-and-neck malignancy, risk of a second head-and-neck primary cancer, treatment cost, and physician and institutional biases.

At the National Cancer Center Hospital, patients with Stage I or II HPC are often treated with RT alone. In this study, we reviewed the data on patients who were treated with RT for early-stage HPC and analyzed the outcomes in these patients.

METHODS AND MATERIALS

Patient characteristics

Between February 1988 and February 2007, 77 patients with Stage I (T1N0M0) or Stage II (T2N0M0) HPC underwent RT in the Division of Radiation Oncology at the National Cancer Center Hospital. These patients consisted of 6 women and 71 men, ranging in age from 42 to 80 years (median, 63 years) (Table 1). All the tumors were diagnosed as squamous cell carcinoma by histopathologic examination of the biopsy specimens, and each tumor was staged retrospectively according to the 2002 UICC TNM classification system based on a complete patient history and physical

Reprint requests to: Ryo-ichi Yoshimura, M.D., Department of Diagnostic Radiology and Oncology, Head and Neck Reconstruction Division, Graduate School, Tokyo Medical and Dental University, 1-5-45, Yushima Bunkyo-ku, Tokyo 113-8519, Japan. Tel: +81) 3-5803-5311; Fax: (+81) 3-5803-0147; E-mail: ysmrmrad@tmd.ac.jp

Conflict of interest: none.

Received Jan 13, 2009, and in revised form May 10, 2009. Accepted for publication June 12, 2009.

Table 1. Patient characteristics

Characteristic	Stage I (n = 42)	Stage II (n = 35)
Sex		
F	2	4
M	40	31
Age (y)		
Range (median)	42–80 (63)	48–79 (63)
HPC site		
Postcricoid region	6	6
Pyriform fossa	30	20
Posterior wall	6	9
Radiotherapy field and dose		
Local	6	5
Dose range (median) (Gy)	60–66 (60)	60–70 (61)
Locoregional	36	30
Primary dose range (median) (Gy)	58–70 (66)	60–70 (66)
Subclinical dose range (median) (Gy)	32–46 (40)	20–50 (40)
Concurrent chemotherapy		
CDDP + 5-FU	10	5
TS-1	1	0

Abbreviations: HPC = hypopharyngeal cancer; CDDP = cisplatin; 5-FU = 5-fluorouracil; TS-1 = tegafur-gimeracil-oteracil potassium.

examination record. The primary sites were the pyriform fossa (PS) in 50 patients (65%), the posterior wall (PW) in 15 (19%), and the postcricoid region (PC) in 12 (16%). At the time when the HPC was found, 21 patients (27%) had symptoms: 12 patients experienced pain in their pharynx, 9 experienced discomfort in their pharynx, and 1 patient experienced a change in his voice (hemilarynx fixation was not observed). Fifty-two patients (68%) were asymptomatic; their HPCs were found by gastrointestinal endoscopy performed as part of a follow-up examination for metachronous malignancies treated before to the diagnosis of HPC in 38 patients (49%: esophageal cancer in 31, gastric cancer in 2, oropharyngeal cancer in 2, oral cancer in 2, and esophageal and gastric cancer in 1), an examination performed before the treatment of some other disease in 10 patients (13%: esophageal cancer in 7, oral cancer in 1, gastric ulcer in 1, and pneumonia in 1), and as part of a general health examination in 4 patients. The symptoms of the remaining 3 patients were not documented.

Treatment

All the patients underwent definitive RT. Either a 4-MV or a 6-MV linac X-ray was used to administer a daily dose of 2 Gy 5 days a week, with a total dosage of 58–70 Gy (median, 66 Gy). A shell was used to immobilize the patient's head, and simulation X-ray radiographs or computed tomography simulation were used to determine the radiation portals and techniques. Local irradiation of the primary site was performed using parallel-opposed lateral fields in 11 patients with a total radiation dose of 60–70 Gy (median, 60 Gy). Elective bilateral neck irradiation was performed in 66 patients using parallel-opposed lateral fields with or without a matched anterior lower neck field or anterior and lateral wedge fields, with a total radiation dose of 20–50 Gy (median, 40 Gy). After the neck irradiation, the radiation to the primary lesion was boosted using a reduced parallel-opposed lateral field, with a total radiation dose of 10–40 Gy (median, 22 Gy).

Chemotherapy was administered concurrently with the RT in 16 patients for the treatment of synchronous cancers (esophageal cancer in 15, and oropharyngeal and laryngeal cancer in 1). Continuous infusions of 5-fluorouracil (5-FU; 600–1,250 mg/day; median, 1,100 mg/day) were given on the first 4 days of weeks 1 and 5 in combination with cisplatin (60–125 mg; median, 110 mg) on the first day of weeks 1 and 5 in the 15 patients with esophageal cancer, and TS-1 (100 mg/day) was successively used for 3 weeks in the 1 patient with oropharyngeal and laryngeal cancers.

Analysis

The median follow-up period was 33 months from the start of RT, ranging between 3 and 229 months. Fifteen patients were observed for less than 12 months: 3 patients died of HPC, 9 died of other cancers, 2 died of unknown reasons, and 1 was alive with another cancer. The median follow-up period for the 35 surviving patients who did not experience a recurrence was 48 months (range,10–229 months.

The overall, HPC-specific, and HPC recurrence-free survival rates and local control rate were calculated using the Kaplan-Meier method. Univariate and multivariate analyses were performed using the log-rank test and the Cox proportional hazards test. A p value of <0.05 and <0.007 was considered statistically significant in the univariate analyses and the multivariate analysis, respectively, resulting in an overall significance level of 5% (3).

Complications were assessed according to the Common Terminology Criteria for Adverse Events v3.0

RESULTS

Survival

The 5-year overall and HPC-specific survival rates for all 77 patients were 47% and 74%, respectively (Fig. 1). Thirty-nine patients died between 3.1 and 191 months (median, 15 months) after the start of RT; the causes of death were HPC in 13 patients who died 11–50 months (median, 15 months) after the start of RT, other malignancies in 16 patients (esophageal cancer in 9, lung cancer in 2, laryngeal

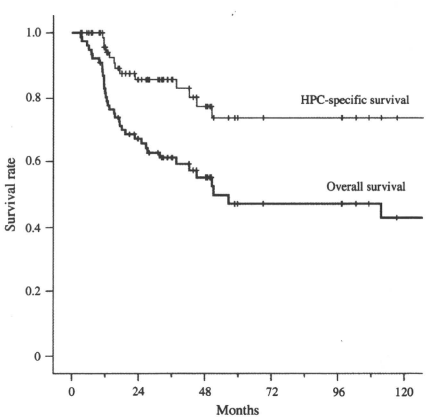

Fig. 1. Overall and hypopharyngeal cancer (HPC)–specific survival for all 77 patients.

Table 2. Overall and HPC-specific survival rates according to patient and clinical factors

Factors		*n*	Overall survival			HPC-specific survival		
			5-year (%)	Univariate *p*	Multivariate *p*	5-year (%)	Univariate *p*	Multivariate *p*
Total		77	47			74		
Sex	F	6	33			40		
	M	71	48	0.27	0.90	76	0.009	0.39
Age (y)	≤65	44	57			72		
	>65	33	34	0.12	0.042	77	0.96	0.60
HPC stage	I	42	52			85		
	II	35	43	0.43	0.18	62	0.024	0.032
HPC site	PC	12	52			59		
	PS	50	53			87		
	PW	15	27	0.052	0.058	43	0.005	0.064
RT field	Local	11	46			56		
	Locoregional	66	48	0.47	0.09	80	0.24	0.18
RT dose:	≤65	35	38			67		
primary (Gy)	>65	42	58	0.12	0.56	83	0.57	0.62
Concurrent CRT	Yes	16	23			69		
	No	61	53	0.085	0.029	74	0.92	0.22

Abbreviations: HPC = hypopharyngeal cancer; RT = radiotherapy; PC = postcricoid region; PS = pyriform fossa; PW = posterior wall; CRT = chemoradiotherapy.

cancer in 1, oropharyngeal cancer in 1, oral cancer in 1, renal cancer in 1, and malignant lymphoma in 1) who died 3.1–191 months (median, 12 months) after the start of RT, and other reasons in 10 patients (infectious pneumonia in 2, heart failure in 1, rupture of an abdominal aortic aneurysm in 1, suicide in 1, and unknown in 5) who died 3.5–57 months (median, 15 months) after the start of RT.

The relations between clinical factors and the overall and HPC-specific survival rates are shown in Table 2. Overall survival was not affected by any patient characteristics or treatment factors. Disease stage and primary site were significant factors for HPC-specific survival in the univariate analysis (disease stage, $p = 0.024$; primary site, $p = 0.005$), and the HPC-specific survival rate in patients with Stage II HPC or a primary site of PC or PW was much lower than that in patients with Stage I or a primary site of PS, but no factors were significant in the multivariate analysis.

Course of HPC

The 5-year HPC recurrence-free survival rate and local control rate with laryngeal voice preservation for all 77 patients were 57% and 70%, respectively (Fig. 2). One patient's tumor remained after RT, 1 patient was diagnosed with lymph node recurrence during RT, and 22 patients experienced disease recurrence 4–51 months (median, 10 months) after the start of RT. Thirteen (54%) of the 24 patients had local recurrences, 8 (33%) had lymph node recurrences, and 3 (13%) had local and lymph node recurrences. Distant metastases were observed in 6 patients (lung in 3, mediastinum in 2, and bone in 1) 11–49 months (median, 19 months) after the start of RT for HPC, but none of these metastases were found before local or lymph node recurrence. The relations between the clinical factors and the HPC recurrence-free survival rate and local control rate with laryngeal voice preservation are shown in Table 3. The HPC recurrence-free survival rate in patients with Stage I HPC or a locoregional RT field was significantly higher than that in patients with Stage II HPC ($p = 0.026$) or a local RT field ($p = 0.036$) in the univariate analysis, but no factors were significantly associated with HPC recurrence-free survival in the multivariate analysis. The primary site and RT field significantly affected the rate of local control with laryngeal voice preservation in the univariate analysis (primary site, $p = 0.036$; RT field, $p = 0.018$), and the local control rate in patients with irradiation of a locoregional field was significantly higher than that in patients with irradiation of a local field in the multivariate analysis ($p = 0.006$).

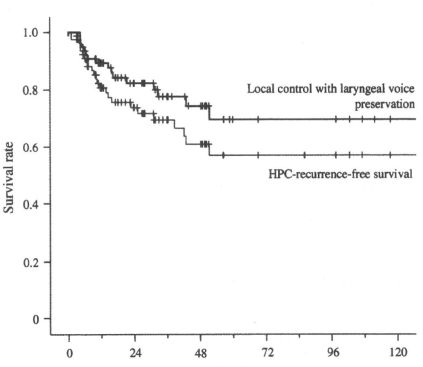

Fig. 2. Hypopharngeal cancer (HPC) recurrence-free survival and local control with laryngeal voice preservation for all 77 patients.

Table 3. HPC recurrence-free survival rate and local control rate with laryngeal voice preservation according to patient and clinical factors

Factors		n	HPC recurrence-free survival 5-year (%)	Univariate p	Multivariate p	Local control with voice preservation 5-year (%)	Univariate p	Multivariate p
Total		77	57			74		
Sex	F	6	50			67		
	M	71	57	0.28	0.90	70	0.35	0.98
Age (y)	≤65	44	49			65		
	>65	33	69	0.36	0.42	79	0.41	0.52
HPC stage	I	42	75			84		
	II	35	41	0.026	0.044	56	0.055	0.048
HPC site	PC	12	47			63		
	PS	50	62			76		
	PW	15	52	0.06	0.18	60	0.039	0.056
RT field	Local	11	38			42		
	Locoregional	66	59	0.036	0.10	73	0.018	0.006
RT dose: primary (Gy)	≤65	35	53			68		
	≥66	42	60	0.78	0.81	72	0.99	0.91
Concurrent CRT	Yes	16	56			83		
	No	61	56	0.4	0.96	68	0.5	0.52

Abbreviations: HPC = hypopharyngeal cancer; RT = radiotherapy; PC = postcricoid region; PS = pyriform fossa; PW = posterior wall; CRT = chemoradiotherapy.

Of 16 patients with local recurrence or local and lymph node recurrence, 12 underwent salvage surgery (total laryngopharyngectomy with or without neck resection in 11 and partial pharyngectomy in 1). One patient underwent chemotherapy, 2 received no treatment, and 1 patient was lost to follow-up after a local recurrence was detected. Of the 8 patients with lymph node recurrence, 6 underwent neck dissection, 1 patient underwent RT, and 1 patient received no treatment. All 3 patients who did not undergo salvage surgery died within 15 months. Only 5 patients with local recurrence and 3 patients with lymph node recurrence responded after surgery, and the 5-year overall survival rate for the 12 patients who were treated with salvage surgery was 39 % (Fig. 3). The difference in overall survival according to salvage therapy was significant ($p = 0.003$).

Of the total of 77 patients, 7 (9%) had Grade 3 or greater complications related to the treatment for HPC, and 6 of these patients experienced their complications after salvage surgery: 2 patients died as a result of arterial injury (Grade 5), 1 had a life-threatening arterial injury (Grade 4), 1 had an arterial injury requiring repair or revision (Grade 3), and 2 developed pharyngeal fistulas requiring operative intervention (Grade 3). One patient who did not have a recurrence developed otitis media with discharge (Grade 3).

Synchronous and metachronous malignancy

Of the 77 patients, 64 (83%) had synchronous or metachronous malignancies; the distribution of these malignancies is shown in Fig. 4. Forty-two had metachronous malignancies diagnosed before they underwent treatment for HPC, and 33 (79%) had esophageal cancer. These malignancies were under control at the start of treatment for HPC, but 19 of these patients had synchronous malignancies and/or metachronous malignancies after RT for HPC.

Overall, 23 patients had synchronous malignancies, 26 had metachronous malignancies after RT for HPC, and 8 had both synchronous and metachronous malignancies. The overall survival rate in the patients whose synchronous and/or metachronous malignancies were detected at an early stage (59% at 5 years) was not different from that in patients without synchronous or metachronous malignancies (48% at 5 years), but the survival rate in the patients whose synchronous or metachronous malignancies were detected at an advanced stage (17% at 5 years) was much lower than that in the patients without synchronous or metachronous malignancies

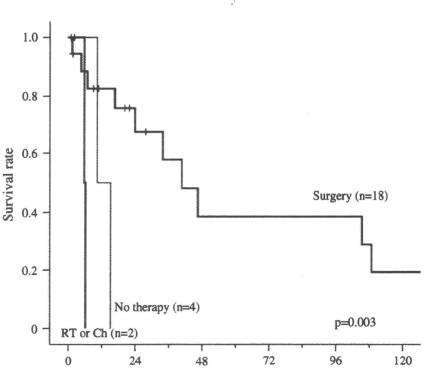

Fig. 3. Overall survival after hypopharyngeal cancer (HPC) recurrence according to salvage therapies (RT = radiotherapy; Ch = chemotherapy).

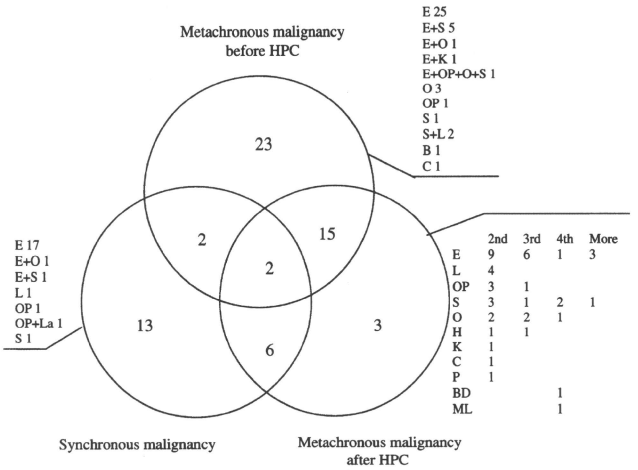

Fig. 4. Number of hypopharyngeal cancer (HPC) patients with synchronous and metachronous malignancy (E = esophagus; S = stomach; O = oral cavity; K = kidney; OP = oropharynx; B = bladder; C = colon; La = larynx; H = liver; P = prostate; BD = bile duct; ML = malignant lymphoma).

or the patients with early-stage synchronous or metachronous malignancies (Fig. 5). Advanced-stage synchronous malignancies were seen in 5 patients with esophageal cancer. All 5 patients received concurrent chemoradiotherapy, but died of their synchronous malignancies 5–13 months (median, 11 months) after the start of RT. Advanced-stage metachronous malignancies were seen in 7 of the 26 patients (lung cancer in 2, oropharyngeal cancer in 2, esophageal cancer in 1, renal cancer in 1, and prostate cancer in 1) 7.5–153 months (median, 12 months) after the start of RT for HPC. Five of these patients died of their advanced-stage metachronous malignancies (lung cancer in 2, oropharyngeal cancer in 1, esophageal cancer in 1, and renal cancer in 1).

The rates of metachronous malignancy after RT for HPC and HPC recurrence after RT, as calculated using the Kaplan-Meier method, are shown in Fig. 6. The rate of HPC recurrence increased rapidly for 2 years after RT and reached a plateau at 4 years. The rate of metachronous malignancy increased year by year after RT. The rate of second primary malignancy was 32% at 5 years and 56% at 10 years, that of third

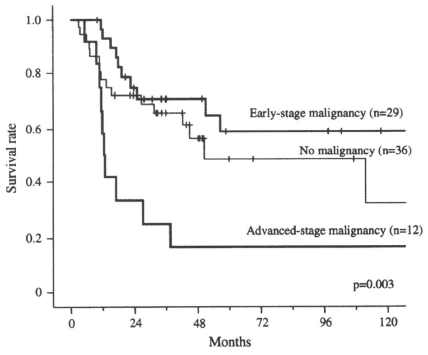

Fig. 5. Overall survival for patients with or without synchronous or metachronous malignancy after radiotherapy for hypopharyngeal cancer (HPC).

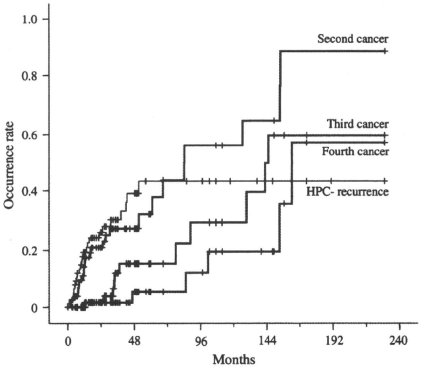

Fig. 6. Rates of hypopharyngeal recurrence and metachronous malignancy after radiotherapy.

malignancy was 15% at 5 years and 29% at 10 years, and that of fourth malignancy was 5% at 5 years and 19% at 10 years.

DISCUSSION

Radiotherapy has long been recognized as effective for early-stage squamous cell carcinoma of the hypopharynx (1, 2). However, few reports have analyzed large numbers of patients undergoing RT for early-stage HPC without lymph node metastasis, and to our knowledge, no reports have statistically analyzed predictors of survival. Concurrent chemoradiotherapy and the computed tomography–based tumor volume have been reported to be strong predictors of local control in HPC patients, including patients with advanced-stage HPC, but whether these factors affect local control or overall survival in patients with early-stage HPC remains unclear (1, 4). In our study, only the RT field significantly affected the local control rate with laryngeal voice preservation in the multivariate analysis, and a locoregional radiation field was appropriate for patients with early-stage HPC. Although disease stage affected the HPC-specific survival rate and the HPC recurrence-free survival rate and the primary site affected the HPC-specific survival rate and the local control rate in univariate analyses, these factors were not significant in a multivariate analysis. The patient and tumor characteristics had no effect on the treatment outcome of RT for early-stage HPC.

Nakamura *et al.* (1) reported the results of an analysis of 115 patients who underwent definitive RT for Stage I and Stage II HPC in a multi-institution study. Their overall and disease-specific survival rates at 5 years were 66% and 77.4%, respectively, and the progression-free survival and local control rates were 67.6% and 76.5% for patients with Stage I, and 51.5% and 62.6% for patients with Stage II at 5 years. Nakamura *et al.* (5) also reported an analysis of 43 other patients who underwent RT with or without salvage surgery for Stage I and II HPC in a single-institution study; the 5-year overall and disease-specific survival rates were 70.4% and 89.5%, respectively. Rabbani et al. (6) analyzed 123 patients with Stage T1–T2N0–N3M0 of the pyriform sinus; the 5-year overall survival, cause-specific survival, and local regional control rate for the 26 patients with T1N0M0 or T2N0M0 HPC were 58%, 85%, and 86%, respectively. In our study, the 5-year HPC-specific survival rate (74%), the HPC recurrence-free survival rate (57%), and the local control rate with laryngeal voice preservation (70%) were similar to these previously reported values, but the 5-year overall survival rate (47%) in our study was lower than the previously reported values (1, 5, 6). We suspect that the larger number of patients with synchronous and metachronous malignancies in the present study may be related to the lower rate of overall survival, compared with the results of previous reports.

The incidence of synchronous and metachronous malignancy in HPC patients has been reported to be approximately 20%, and the most common sites were the lung, the esophagus, and the urinary tract (7, 8). However, patients with early-stage primary tumors have a higher risk of developing a second primary tumor than do patients with advanced tumors because of their longer survival period (7); Nakamura et al. (1, 5) reported that the incidence of synchronous or metachronous malignancy in patients with early-stage HPC was 46.5–56.5%. In our study, 83% (64/77) of the patients had synchronous and/or metachronous malignancy and 53% (41/77) had synchronous malignancy and/or metachronous malignancy after RT for HPC; most of these malignancies were esophageal cancer. Because 54% (42/77) of these patients had a history of treatment for malignancy before the diagnosis of HPC, individual and/or environmental factors might have contributed to the formation of the multiple primary tumors in many of these patients (7). However, the overall survival rate for patients with early-stage synchronous malignancy and/or metachronous malignancy after RT for HPC was similar to that for patients without these malignancies, but the overall survival rate for patients with advanced-stage synchronous malignancy or metachronous malignancy after RT for HPC was significantly poorer. A more careful follow-up for detection of early-stage metachronous malignancy might have improved the overall survival rate in the present study.

The detection of early-stage HPC is as difficult as the detection of early-stage esophageal cancer, but the development of endoscopy has made both of these conditions detectable (9). In our study, HPC was diagnosed during gastrointestinal endoscopy examinations performed as pretreatment or follow-up examinations for other malignancies in 62% (48/77) of the patients. Recently, narrow band imaging has been reported to improve the diagnostic accuracy and sensitivity at which early-stage HPC can be detected (10). However, endoscopy techniques (*i.e.,* endoscopic laser resection) have been used only in a few institutions, and the indication for these treatments is unclear (9, 11). Although Shimizu *et al.* (9) performed endoscopic submucosal dissection in 4 patients with early-stage HPC and reported no local recurrences, no distant metastasis, and no early or late complications, Bernal-Sprekelsen *et al.* (11) performed endoscopic resection using a CO_2 laser and reported the need for a nasogastric feeding tube in 23.2% of the patients with small tumors, postoperative pneumonia in 5.7%, temporary postoperative coughing during oral intake in 28.1%, and severe swallowing difficulties in 3.8%. Thus, the factors associated with the occurrence and severity of various complications after endoscopic resection remain to be clarified (9).

In the present study, because we retrospectively analyzed the data of patients who underwent RT for early-stage HPC, we could not exclude some potential biases and study limitations from our results. However, we believe that RT is an appropriate treatment method for early-stage HPC, compared with surgical resection, because the outcome of RT was not affected by the patient or tumor characteristics in the present study, and cosmetic defects, swallowing disorders, aspiration pneumonia, and speech defects were avoided. Patients with early-stage HPC have a high risk of synchronous and metachronous malignancy, and their prognosis heavily depends on the development of such malignancies. However, if such malignancies are detected at an early

stage, patients whose HPC was treated using RT are often able to receive sufficient treatment for those malignancies, and their overall survival rate is as high as that in patients without these malignancies (1, 5, 6, 9). Patients with early-stage HPC should be carefully examined before and after the start of treatment and should be closely followed up at frequent intervals to ensure the early detection of synchronous and metachronous malignancies (7).

REFERENCES

1. 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;65:1045–1050.
2. Foote RL. Radiotherapy alone for early-stage squamous cell carcinoma of the larynx and hypopharynx. *Int J Radiat Oncol Biol Phys* 2007;69:S31–S36.
3. Beck-Bornholdt HP, Dubben HH. Potential pitfalls in the use of *p*-values and interpretation of significance levels. *Radiother Oncol* 1994;33:171–176.
4. Shang-Wen C, Shih-Neng Y, Ji-An L, *et al.* Value of computed tomography-based tumor volume as a predictor of outcomes in hypopharyngeal cancer after treatment with definitive radiotherapy. *Laryngoscope* 2006;116: 2012–2017.
5. Nakamura K, Shioyama Y, Sasaki T, *et al.* Chemoradiation therapy with or without salvage surgery for early squamous cell carcinoma of the hypopharynx. *Int J Radiat Oncol Biol Phys* 2005;62:680–683.
6. Rabbani A, Amdur RJ, Mancuso AA, *et al.* Definitive radiotherapy for T1-T2 squamous cell carcinoma of pyriform sinus. *Int J Radiat Oncol Biol Phys* 2008;72:351–355.
7. Raghavan U, Quraishi S, Bradley PJ. Multiple primary tumors in patients diagnosed with hypopharyngeal cancer. *Otolaryngol Head Neck Surg* 2003;128:419–425.
8. Kohmura T, Hasegawa Y, Matsuura H, *et al.* Clinical analysis of multiple primary malignancies of the hypopharynx and esophagus. *Am J Otolaryngol* 2001;22:107–110.
9. Shimizu Y, Yamamoto J, Kato M, *et al.* Endoscopic submucosal dissection for treatment of early stage hypopharyngeal carcinoma. *Gastrointest Endosc* 2006;64:255–259.
10. Watanabe A, Taniguchi M, Tsujie H, *et al.* The value of narrow band imaging endoscope for early head and neck cancers. *Otolaryngol Head Neck Surg* 2008;138:446–451.
11. Bernal-Sprekelsen M, Vilaseca-Gonzalez I, Blanch-Alejandro JL, *et al.* Predictive values for aspiration after endoscopic laser resections of malignant tumors of the hypopharynx and larynx. *Head Neck* 2004;26:103–110.