ANTICANCER RESEARCH *41*: 5761-5766 (2021)
doi:10.21873/anticanres.15392

Prognostic Factors of Potential Early Recurrence of Hypopharyngeal Carcinoma

DAISUKE BABA[1], CHIHIRO FUSHIMI[2], KENJI HANYU[2], TATSUO MASUBUCHI[2], YUICHIRO TADA[2] and KOKI MURA[2]

[1]*Department of Head and Neck Surgery, National Cancer Center Hospital East, Chiba, Japan;*
[2]*Department of Head and Neck Oncology, International Health and Welfare Mita Hospital, Tokyo, Japan*

Abstract. *Background/Aim: Prognostic factors of hypopharyngeal carcinoma have been reported previously. However, recurrent cases of this disease occurring within 6 months of treatment have been excluded or poorly documented in many studies. We aimed to evaluate the prognostic factors of hypopharyngeal carcinoma recurrence within 6 months. Patients and Methods: A total of 120 patients were eligible for this retrospective study. Recurrent cases of hypopharyngeal carcinoma occurring within 6 months of treatment were evaluated and compared with non-recurrent cases. Results: Recurrence within 6 months was detected in 28/50 cases. In univariate analyses, classification markers (pT≥4a and cN≥2b) were statistically significant prognostic factors for early recurrence (p=0.04 and p=0.04, respectively); however, only pT≥4a was predictive of recurrence in multivariate analyses (p=0.02). Conclusion: Risk stratification according to the prognostic factor pT≥4a will allow physicians to identify patients who should be followed meticulously within the first 6 months.*

The worldwide annual incidence of hypopharyngeal carcinoma is approximately 84,000 cases, accounting for about 5% of head and neck cancers; the associated annual mortality is nearly half of the incidence rate (1). The main causes of poor prognosis are the complex anatomy of the hypopharynx, rich lymphatic drainage, and late appearance of symptoms that affects the timing of diagnosis (2, 3).

An appropriate follow-up strategy, especially during the first 6 months after treatment completion, is important for improving the survival in patients with hypopharyngeal squamous cell carcinoma due to the potential early detection of recurrence. However, existing guidelines and recommendations regarding follow-up method are not sufficiently evidence based; few prospective studies have examined survival of hypopharyngeal squamous cell carcinoma (4, 5). For example, it is recommended that follow-up after treatment completion should be performed every 1-3 months during the first year, every 2-6 months during the second year, and every 4-8 months during the third to fifth year (4). However, most studies, including those forming the basis for these guidelines, are retrospective studies with an insufficient number of patients with hypopharyngeal carcinoma. Thus, there is currently no consensus on the best follow-up method for this disease (6-8).

Moreover, there is little evidence for establishing a follow-up strategy within 6 months of treatment completion because many studies excluded recurrent cases detected within 3-6 months of treatment completion to avoid including residual cases inadvertently (7-9). In medical practice, differentiating between a residual tumour and recurrence immediately after treatment completion is challenging in some cases, and doctors' opinions may differ. All patients must be followed up meticulously for recurrence, especially for possible residual cases (4). This is particularly true for patients with hypopharyngeal carcinoma in whom early recurrence and mortality after treatment are more common than in those with recurrence of many other cancer types (2). For example, the reported median follow-up time to relapse of hypopharyngeal carcinoma is 8.3 months in Japan (10). Thus, an appropriate follow-up strategy for the detection of early recurrence, especially during early periods which were excluded in most previous studies, is required to ensure the success of salvage treatment, patient survival, and quality of life.

Hence, we aimed to evaluate risk factors of early recurrence of hypopharyngeal carcinoma occurring within 6 months of treatment.

Correspondence to: Dr. Chihiro Fushimi, Department of Head and Neck Oncology, International Health and Welfare Mita Hospital, 1-4-3 Mita, Minato-ku, Tokyo, Japan. Tel: +81 334518121, Fax: +81 334540067, e-mail: chihiro.fushimi@iuhw.ac.jp

Key Words: Early recurrence, follow-up, hypopharyngeal carcinoma, prognostic factor.

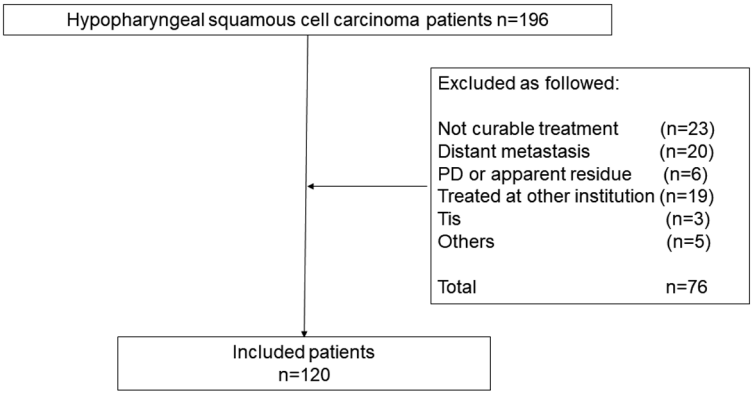

Figure 1. *Flowchart of the patient selection process.*

Patients and Methods

Ethics review. This study was approved by the Institutional Review Board of the International Health and Welfare Mita Hospital (No. 52084). Written informed consent was obtained from all patients at their first visit. This study was conducted in accordance with the provisions of the Declaration of Helsinki.

Study population. We evaluated data of 196 patients with hypopharyngeal cancer who presented at the International Health and Welfare Mita Hospital, Tokyo, Japan, between January 1, 2012, and December 31, 2018.

The eligibility criteria were as follows: >18 years of age, a squamous cell carcinoma diagnosis, and no previous treatment for hypopharyngeal carcinoma. The exclusion criteria were as follows: no administered curative treatment, distant metastatic disease at initial diagnosis, patients with carcinoma who had disease progression or apparent residual tumour at the end of the treatment, and carcinoma *in situ*. Consequently, 120 patients were enrolled (Figure 1).

Patient demographics and clinical characteristics. We retrospectively analysed the medical records of eligible patients, extracting data on age, sex, subsite of the carcinoma, Tumor–Node–Metastasis (TNM) classification, treatment method, and pathological findings. TNM classification and pathological findings were re-evaluated using medical records and images, according to the criteria described in the Unio Internationalis Contra Cancrum staging manual, 8th edition (11). We also extracted survival and recurrence data from patient medical records. Recurrence-free survival (RFS) was defined as the period from the date the treatment was completed to the date recurrence was detected or when follow-up was discontinued because of self-decision or death.

Treatment methods. A multidisciplinary cancer board comprising head and neck oncologists, pathologists, radiologists, dentists, and nurses chose the treatment method for each patient. Briefly, patients with clinical stage III or IV were treated using curative tumour resection unless patients desired organ-preservation treatment. Based on the pathological findings and regardless of the tumour pathological stage, radiation therapy (RTx) and chemotherapy (CTx) were added, if extranodal extension (ENE), a positive margin, retropharyngeal node metastasis, or invasion of the prevertebral muscle were detected. In patients with clinical stage I, organ-preserving treatment (such as transoral surgery and/or RTx) was selected. In patients with clinical stage II, CTx was administered when RTx was selected. In some patients with T1 or T2 stage and nodal metastasis suspected of ENE, transoral surgery was conducted, followed by concomitant chemoradiotherapy (CCRT) according to each doctor's decision. Similarly, in some patients with advanced T stage and without nodal metastasis where ENE was definitely denied clinically, neck dissections were conducted, followed by CCRT if patients wished to preserve their larynx. Such patients were designated "CCRT" in the characteristics of the treatment group. Cisplatin (CDDP), administered every three weeks at 80 mg/m^2, was only used in patients with normal renal function who underwent RTx. Patients aged ≥70 years were not considered tolerant to CTx and were therefore not treated with CTx.

Follow-up strategy. In our institution, patients were followed up at the outpatient department after completion of the treatment for hypopharyngeal carcinoma. All patients re-visited our department every month during the first year, every two months during the second year, four times a year during the third to fifth year post-treatment, and then one or two times a year up to 10 years post-treatment, if the risk of recurrence was considered high. A clinical examination with endoscopy of the pharynx and ultrasonography was performed during each follow-up visit. Computed tomography (CT) was performed within 3 months of treatment and every 3 months during the first year, every 6 months during the second year, and then once a year for the rest of post-treatment follow-ups. Positron emission tomography with CT (PET-CT) was generally conducted between 3 and 6 months of treatment. After this initial scan, PET-CT was conducted only when recurrence was suspected.

In cases when residual hypopharyngeal carcinoma could not be ruled out, CT was performed within 1 month of treatment completion. Cases for which residual hypopharyngeal carcinoma could not be ruled out during the one-month follow-up had a repeat CT performed during the next month's visit. These patients were also evaluated using PET-CT after 3 months of treatment completion. The diagnosis of recurrence was based on a biopsy-confirmed malignant tumour or findings supportive of recurrence

Table I. *Patient demographic characteristics and medical history.*

Variables		N (%)	Variables		N (%)
Age	≥70	46 (38)	Neoadjuvant CTx	–	110 (92)
Gender	Men	108 (90)		DCS	9 (8)
Subsite	PS	87 (72)		Others	1 (1)
	PC	20 (17)	pT	1	6 (9)
	PW	13 (11)		2	25 (38)
cT	1	19 (16)		3	20 (31)
	2	48 (40)		4a	13 (20)
	3	33 (28)		4b	1 (2)
	4a	19 (16)	pN	0	13 (19)
	4b	1 (1)		1	10 (15)
cN	0	42 (35)		2a	0 (0)
	1	16 (13)		2b	11 (16)
	2a	3 (3)		2c	5 (7)
	2b	27 (23)		3a	0 (0)
	2c	9 (8)		3b	28 (42)
	3a	1 (1)	Margin	Negative	58 (89)
	3b	22 (18)		Positive	7 (11)
cStage	1	12 (10)	ENE	–	26 (48)
	2	14 (12)		+	28 (52)
	3	25 (21)	Postope	–	44 (68)
	4a	46 (38)	CCRT	+	21 (32)
	4b	23 (20)		Mean Rtxdose (SD)	65.1 (3.26)
Surgery	TPL	57 (48)		CTx –	4 (19)
	Partial pharyngectomy	2 (2)		CDDP	13 (62)
	TOVS/ELPS	10 (8)		Cmab	3 (14)
	ND	7 (6)		Others	1 (5)
CCRT	+	54 (45)			
	Mean Rtxdose (SD)	65.4 (4.6)			
	CTx –	5 (9)			
	CDDP	26 (48)			
	Cmab	18 (33)			
	Others	5 (9)			

on CT, magnetic resonance imaging (MRI), or PET-CT when a biopsy could not be performed safely.

Statistical analysis. All statistical analyses were conducted using EZR software (EZR version 1.54, Saitama, Japan). The RFS was estimated using the Kaplan–Meier method. The prognostic factors of clinical or pathological TNM classification and age were divided into two groups. The prognostic factors (*i.e.*, group of age, sex, treatment method, group of clinical or pathological TNM classification, and pathological findings) were evaluated using the χ^2 test. We conducted multivariate regression analyses with logistic regression tests, adjusting for variables that were statistically significant in the univariate analyses. A two tailed p-value <0.05 was considered statistically significant.

Results

Participant characteristics and treatment information. A total of 120 patients were eligible for this study. Patient characteristics at baseline are shown in Table I.

The median age at initial presentation was 67 years (range=60-73 years), and the patients were predominantly male (108/120 patients). The major subsite of the tumour was the piriform sinus (87/120 patients). The majority of patients had advanced-stage disease (stage III or IV). The median RTx dose for patients with CCRT and post-operative radiation was 66 Gy. CDDP was mainly administered when chemotherapy was complete. The median follow-up period for these patients was 23.8 months (range=6.8-41.5 months).

Recurrence patterns. The median time from completing treatment to recurrence was 4.9 months (range=2.9-13.8 months). Most patients experienced a recurrence within 2 years of treatment (46/50 patients). The Kaplan–Meier curve of RFS is shown in Figure 2. We found that the recurrence rate was increased rapidly within 6 months after completing treatment. Recurrence according to post-treatment duration is shown in Figure 3. Twenty-eight of 50 patients had a recurrence or residual tumour within 6 months. Among these patients, 17 developed loco-regional recurrence, and 14 developed distant metastasis. Lung metastasis, observed in nine patients, was the most common recurrence.

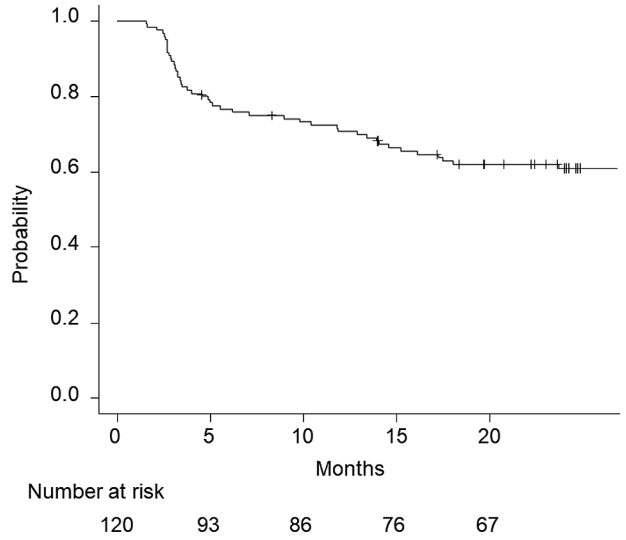

Figure 2. *Kaplan–Meier curve of recurrence-free survival in patients with hypopharyngeal carcinoma.*

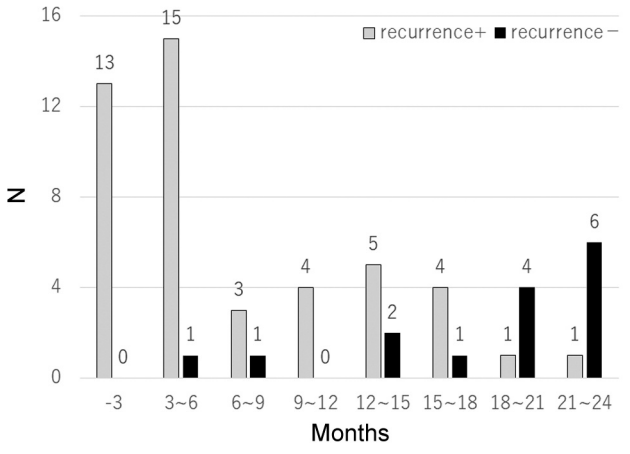

Figure 3. *Distribution of recurrence within a 3-month window in patients with hypopharyngeal carcinoma.*

Prognostic factors. In univariate analyses, pT4a and 4b (pT≥4) and cN2b, 2c, 3a, and 3b (cN≥2b) were significant prognostic factors for early recurrence or the presence of residual tumour of hypopharyngeal carcinoma within 6 months of treatment completion (Table II). The odds ratios (OR) were 4.6 (p=0.04) and 2.7 (p=0.04), respectively.

Multivariate models comprised variables that were significant in the univariate analyses, and the results are shown in Table III. Only pT≥4a was a significant prognostic factor for the recurrence or presence of residual tumours within 6 months of treatment completion; the OR was 5.0 (p=0.02).

Discussion

In this study, we evaluated the frequency of hypopharyngeal tumour recurrence and the presence of residual tumour within 6 months of treatment completion, with results sorted according to the duration of the post-treatment period. In 28 of 50 patients, tumour recurrence was detected within 6 months of treatment completion. In addition, we examined the prognostic factors for early recurrence and the possibility of a residual tumour. In univariate analyses, both pT≥4a and cN≥2b were statistically significant prognostic factors for early recurrence or presence of tumour residue. In multivariate analyses, only pT≥4a was a significant prognostic factor.

According to the National Comprehensive Cancer Network (NCCN) guidelines, it is recommended that follow-up should be performed every 1-3 months during the first year after treatment completion, and imaging studies (such as CT or MRI) should be performed 1-2 months following treatment completion. PET-CT is also recommended within 6 months. However, most studies that formed the basis for these guidelines did not provide sufficient evidence. In most studies of hypopharyngeal carcinoma follow-up, recurrent cases occurring within 3-6 months of treatment completion were excluded because residual tumours or synchronous cancers could not be ruled out within this timeframe (7-9). In medical practice, however, it may be difficult to distinguish scars or inflammation from residual tumours or recurrence. Hence, high frequency follow-up visits and imaging studies are required. Regarding PET-CT, there is a general consensus in the NCCN guidelines and in other studies that fluoro-2-deoxy-D-glucose PET/CT should be performed 3-6 months after RT (4). However, the accuracy of this procedure is not high within the 3-6 months after treatment completion, with reported positive predictive value ranges of 27.3-50, 48.4-58.3, and 71.4-100% for the diagnosis of recurrence after 0-3, 3-6, and 6-12 months post-treatment, respectively (12). Thus, it is reasonable to suggest an improved follow-up modality at 6 months (rather than 3 months) post-treatment.

Previous studies have shown that early recurrence of hypopharyngeal carcinoma is common. The reported median follow-up time to relapse was 8.3-12.5 months among patients with hypopharyngeal carcinoma (6, 10). In our study, the median follow-up time to relapse was only 4.9 months, with 56% of disease recurrence occurring within 6 months. Therefore, our study showed earlier recurrent cases than previous studies did. This may be because many of the patients in our study were in an advanced carcinoma stage upon treatment (70/120 patients had stage IV disease). These results reinforce the importance of a follow-up strategy focusing on the first 6 months after treatment completion, particularly in patients with advanced-stage disease.

Table II. *Odds ratios for prognostic factors for carcinoma recurrence within 6 months of treatment completion in the univariate analyses.*

Variables		OR	95%CI	*p*-Value
Age	<70	Ref		
	≤70	2.3	0.9-5.9	0.09
Sex	Men	Ref		
	Women	1.7	0.4-7.2	0.6
cStage	≥III	Ref		
	≤IVa	2.7	0.99-8.4	0.05
cT classification	≤3	Ref		
	≤4a	1.1	0.3-3.7	1
cN classification	≥2a	Ref		
	≤2b	2.7	1.04-7.6	0.04
Neoaduvant CTx	–	Ref		
	+	2.4	0.6-9.9	0.3
Treatment	ope±RTx	Ref		
	CCRT	1.5	0.6-3.9	0.4
ENE	–	Ref		
	+	3	0.6-20.0	0.2
Margin	–	Ref		
	+	3.5	0.4-24.5	0.1
Post operation Rtx	–	Ref		
	+	0.9	0.2-3.9	0.8
pT classification	≤3	Ref		
	≤4a	4.6	1.00-21.3	0.04
pN classification	≥2a	Ref		
	≤2b	7.7	0.99-354	0.06

CI: Confidence interval; OR: odds ratio; cN: clinical N stage; cT: clinical T stage; CTx: chemotherapy; ENE: extranodal extension; pT: pathological T stage; Rtx: radiation therapy; pN: pathological N stage; CCRT: concomitant chemoradiotherapy.

Table III. *Odds ratios for prognostic factors for carcinoma recurrence within 6 months of treatment completion in the multivariate analyses.*

Variables		OR	95%CI	*p*-Value
pT classification	≤3	Ref		
	≤4a	5	1.3-20.2	0.02
cN classification	≥2a	Ref		
	≤2b	3.9	0.9-16.7	0.07

CI: Confidence interval; OR: odds ratio; pT: pathological T stage; cN: clinical N stage.

Some previous reports have shown several prognostic factors for hypopharyngeal carcinoma recurrence, including age, TNM classification, the Charlson Comorbidity Index, and treatment methods (3, 13). However, to the best of our knowledge, there is no previous study on the prognosis of early recurrence of hypopharyngeal carcinoma, especially as early as 6 months post-treatment. We found that a pT≥4a and cN≥2b were significant prognostic factors in the univariate analyses, and only pT≥4a was a significant prognostic factor for early recurrence in multivariate analyses. To the best of our knowledge, this is also the first study to compare recurrence of hypopharyngeal carcinoma at or before 6 months post-treatment with later recurrence or non-recurrence cases. Risk stratification according to the prognostic factor pT≥4a will allow physicians to choose more appropriate follow-up methodologies within the first six months of treatment completion.

A limitation of our study was the retrospective design, which may have caused diagnosis bias especially in re-staging performed based on limited information from medical records and imaging data; thus, the staging might not have been adequately representative. In addition, this study included a small number of patients from only one institution. Therefore, the results may lack generalizability and thus should be interpreted cautiously. Further, this study included only clinical data, while in recent studies, some proteins were proven to be prognostic factors for head and neck carcinoma; thus, not all possible prognostic factors were analysed (14, 15).

Despite these limitations, this study indicated that a more efficient follow-up strategy according to the risk stratification could be employed. Future studies should include more patients and additional prognostic factors for a greater statistical power to thoroughly evaluate risk stratification for each recurrence pattern with regard to follow-up methods.

Conflicts of Interest

The Authors declare no conflicts of interest associated with this manuscript.

Authors' Contributions

DB, CF, TM, YT and KM contributed significantly to the conception and design. DB, KH and CF collected and analysed the clinical data. DB, KH and CF contributed to writing, review and/or revision of the manuscript. CF, TM, YT and KM supervised the manuscript. All Authors have read and approved the final manuscript.

Acknowledgements

The Authors would like to thank Takuro Okada, Tatsuya Kitajima, and Tomoo Shibasaki for collecting clinical data.

References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *71(3)*: 209-249, 2021. PMID: 33538338. DOI: 10.3322/caac.21660

2 Visini M, Giger R, Shelan M, Elicin O and Anschuetz L: Predicting factors for oncological and functional outcome in hypopharyngeal cancer. Laryngoscope *131(5)*: E1543-E1549, 2021. PMID: 33098325. DOI: 10.1002/lary.29186

3 Lin H, Wang T, Heng Y, Zhu X, Zhou L, Zhang M, Shi Y, Cao P and Tao L: Risk stratification of postoperative recurrence in hypopharyngeal squamous-cell carcinoma patients with nodal metastasis. J Cancer Res Clin Oncol *147(3)*: 803-811, 2021. PMID: 32728810. DOI: 10.1007/s00432-020-03337-0

4 Pfister DG, Spencer S, Adelstein D, Adkins D, Anzai Y, Brizel DM, Bruce JY, Busse PM, Caudell JJ, Cmelak AJ, Colevas AD, Eisele DW, Fenton M, Foote RL, Galloway T, Gillison ML, Haddad RI, Hicks WL, Hitchcock YJ, Jimeno A, Leizman D, Maghami E, Mell LK, Mittal BB, Pinto HA, Ridge JA, Rocco JW, Rodriguez CP, Shah JP, Weber RS, Weinstein G, Witek M, Worden F, Yom SS, Zhen W, Burns JL and Darlow SD: Head and neck cancers, version 2.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw *18(7)*: 873-898, 2020. PMID: 32634781. DOI: 10.6004/jnccn.2020.0031

5 Cohen EE, LaMonte SJ, Erb NL, Beckman KL, Sadeghi N, Hutcheson KA, Stubblefield MD, Abbott DM, Fisher PS, Stein KD, Lyman GH and Pratt-Chapman ML: American Cancer Society head and neck cancer survivorship care guideline. CA Cancer J Clin *66(3)*: 203-239, 2016. PMID: 27002678. DOI: 10.3322/caac.21343

6 Ng SP, Pollard C 3rd, Berends J, Ayoub Z, Kamal M, Garden AS, Bahig H, Cantor SB, Schaefer AJ, Ajayi T, Gunn GB, Frank SJ, Skinner H, Phan J, Morrison WH, Ferrarotto R, Johnson JM, Mohamed ASR, Lai SY, Hessel AC, Sturgis EM, Weber RS, Fuller CD and Rosenthal DI: Usefulness of surveillance imaging in patients with head and neck cancer who are treated with definitive radiotherapy. Cancer *125(11)*: 1823-1829, 2019. PMID: 30748005. DOI: 10.1002/cncr.31983

7 Hall SF, Owen T, Griffiths RJ and Brennan K: Does the frequency of routine follow-up after curative treatment for head-and-neck cancer affect survival? Curr Oncol *26(5)*: 295-306, 2019. PMID: 31708648. DOI: 10.3747/co.26.4949

8 Gore A, Baugnon K, Beitler J, Saba NF, Patel MR, Wu X, Boyce BJ and Aiken AH: Posttreatment imaging in patients with head and neck cancer without clinical evidence of recurrence: Should surveillance imaging extend beyond 6 months? AJNR Am J Neuroradiol *41(7)*: 1238-1244, 2020. PMID: 32554418. DOI: 10.3174/ajnr.A6614

9 Kytö E, Haapio E, Minn H and Irjala H: Critical review of the follow-up protocol for head and neck cancer patients. J Laryngol Otol *133(5)*: 424-429, 2019. PMID: 31006389. DOI: 10.1017/S0022215119000811

10 Japan Society for Head and Neck Cancer: Report of head and neck cancer registry of Japan: five-year prognosis of patients registered in 2012. Available at: http://www.jshnc.umin.ne.jp/pdf/2012syourei_yogo.pdf [Last accessed on September 1, 2021]

11 Brierley JD, Gospodarowicz MK and Wittekind C: TNM classification of malignant tumours, 8th ed. Chichester: Wiley-Blackwell, 2017.

12 Risør LM, Loft A, Berthelsen AK, Loft FC, Madsen AR, Vogelius IR, Kjær A and Friborg J: FDG-PET/CT in the surveillance of head and neck cancer following radiotherapy. Eur Arch Otorhinolaryngol *277(2)*: 539-547, 2020. PMID: 31646385. DOI: 10.1007/s00405-019-05684-2

13 Väisänen JA, Alho OP, Koivunen PT and Läärä E: Cause-specific mortality in patients with head and neck cancer: Long-term follow-up of a population-based cohort from 1986 to 2012 accounting for competing risks. Oral Oncol *79*: 20-26, 2018. PMID: 29598946. DOI: 10.1016/j.oraloncology.2018.02.008

14 Meng X, Matsumoto F, Mori T, Miura N, Ino Y, Onidani K, Kobayashi K, Matsuzaki Y, Yoshimoto S, Ikeda K and Honda K: BP180 is a prognostic factor in head and neck squamous cell carcinoma. Anticancer Res *41(2)*: 1089-1099, 2021. PMID: 33517320. DOI: 10.21873/anticanres.14867

15 Ernst BP, Mikstas C, Stöver T, Stauber R and Strieth S: Association of eIF4E and SPARC expression with lymphangiogenesis and lymph node metastasis in hypopharyngeal cancer. Anticancer Res *38(2)*: 699-706, 2018. PMID: 29374693. DOI: 10.21873/anticanres.12275

Received August 31, 2021
Revised October 19, 2021
Accepted October 20, 2021