Predisposing Factors for Larynx Preservation Strategies with Non-surgical Multimodality Treatment for Locally Advanced (T3-4) Larynx, Hypopharynx and Cervical Esophageal Disease

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Abstract. *Aim: To identify predisposing factors for larynx preservation strategies using non-surgical multimodality approaches. Patients and Methods: We retrospectively reviewed the records of 48 patients with T3-4 diseases (14 larynx, 19 hypopharynx, 15 cervical esophagus). Out of 48 patients, 33 refused surgery, and 15 were deemed inoperable, and a total of 25 were graded as T3 and 23 as T4. A total of 24 patients received induction chemotherapy. Radiotherapy was administered at a median dose of 61 Gy (range, 30-71 Gy). Concurrent chemotherapy was administered to all patients: intra-arterial infusion in 21, systemic infusion in 24, or both in 3. Results: Thirty-seven cases (77%) achieved a complete response. The 3-year local control, progression-free survival (PFS), overall survival (OS), and laryngeal preservation rates were 56%, 48%, 56%, and 73%, respectively. Tumor location, nodal involvement, and pre-treatment serum hemoglobin values were identified as predisposing factors for local control, PFS, and OS. Multivariate analysis revealed that the pre-treatment serum hemoglobin levels and tumor location were significant prognostic factors for PFS. Conclusion: Tumor location and pre-treatment hemoglobin levels are important prognostic factors for PFS for non-surgical multimodal organ preservation treatment.*

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Historically, the standard choice of treatment for advanced hypopharynx, larynx, and cervical esophageal carcinoma has been surgical resection, including laryngectomy with or without adjuvant radiotherapy. However, substantial impairment of quality of life after surgical resection has driven the advancement of enhanced organ conservative techniques. Thus far, several alternative techniques to preserve organ shape and function in cancer surgery have been explored. Out of these, induction chemotherapy followed by radiotherapy (RT) has been shown to produce survival equivalent to laryngectomy following RT (1). The results of previous randomized trials and meta-analyses (2-4) of patients with larynx or hypopharynx squamous cell carcinoma comparing the outcomes of total laryngectomy with induction chemotherapy followed by RT in good responders or total laryngectomy alone in poor responders indicated that induction chemotherapy with cisplatin–fluorouracil (PF) did not jeopardize overall survival (OS), and the larynx was preserved in 56% patients. Accordingly, at our institution, we adopted these strategies to improve outcomes of nonsurgical treatments, not only induction chemotherapy (5) but also in combination with intra-arterial infusion chemotherapy, to maximize the efficacy of chemoradiotherapy without hampering organ function (6-8). Herein we present the outcomes of a non-surgical multimodal larynx-preserving approach for the treatment of T3-4 hypopharynx, larynx, and cervical esophageal carcinoma and identify predisposing factors of treatment outcome.

Patients and Methods

Patients and inclusion criteria. We retrospectively reviewed the medical records of 48 patients (median age, 67 years; range, 44-86 years) with nonmetastatic squamous cell cancer of the larynx (n=14), hypopharynx (n=19), or cervical esophagus (n=15) who

Table I. *Patients' characteristics*.

Variables	Strata	
Gender	Male	42
	Female	6
Age, years	Median (range)	67 (44-86)
Site	Larynx	14
	(glottis: supraglottis)	(6 : 8)
	Hypopharynx	19
	(pyriform sinus: posterior wall: postcricoid)	(16: 2: 1)
	Cervical esophagus	15
T category	3	25
	(Larynx : Hypopharynx : Esophagus)	(11 : 10 : 4)
	4	23
	(Larynx : Hypopharynx : Esophagus)	(3 : 9 : 11)
N category	0	22
	1-	26
	Larynx and hypopharynx (N0 : N1:N2:N3)	(18 : 0 : 14 : 1)
	Cervical esophagus (N0 : N1)	(4 : 11)
Stage	II	3
	(Larynx : Hypopharynx : Esophagus)	(0: 0: 3)
	III	24
	(Larynx : Hypopharynx : Esophagus)	(10 : 2 : 12)
	IV	21
	(Larynx : Hypopharynx : Esophagus)	(4 : 17 : 0)
Hemoglobin level	median (range)	12.2 g/dL (7.9-15.9 g/dL)
Operability	Operable	33
	Inoperable	15
Intra-arterial infusion chemotherapy	Yes	21
	No	27
Neoadjuvant chemotherapy	Yes	24
	No	24

refused surgery or with nonresectable disease and received a definitive multimodality treatment at the Kurume University Hospital between 2002 and 2011. Patients' characteristics are summarized in Table I. Tumors were staged according to the sixth edition of TNM Classification of Malignant Tumours (Union for International Cancer Control) as follows: T3, n=25; T4, n=23; and lymph node-positive, n=26.

Therapy protocols. External-beam radiotherapy (median, 61 Gy; range, 30-71 Gy) was administered 5-10 times a week in once-daily (1.8-2.0 Gy/day) or twice-daily fractions (1.6 Gy + 0.8 Gy or 1.2 Gy twice) using a 4-6-MV photon beam produced by a Linac MHCL 15DP linear accelerator (Mitsubishi Corporation, Tokyo, Japan). A radiation planning system for 3D conformal RT was used to schedule treatments as described elsewhere (5). In brief, radiotherapy was initially administered, including prophylactic radiation fields of up to 40-46 Gy. Treatment for the primary lesion involving neck nodes was further boosted to 60-70 Gy to spare the spinal cord outside of the prophylactic area. The gross tumor volume was defined as the total volume of the primary lesion and the involved lymph nodes as determined by laryngoscopy, computed tomography (CT), magnetic resonance imaging (MRI), and 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) positron-emission tomography (PET). A positive lymph node was defined as >10 mm in the short axis on CT/MRI or positive by ^{18}F-FDG PET findings.

Of the 48 patients, 24 (50%) received multi-agent induction chemotherapy consisting of cisplatin (CDDP) and 5-fruorouracil (5-FU) (FP) and/or CDDP and 5-FU and docetaxel. Patients who achieved a partial response received computer-controlled radiation therapy with concurrent chemotherapy, intra-arterial infusion chemotherapy, or CDDP or FP. The remaining 24 (50%) patients received non-induction chemotherapy. All patients received concurrent chemoradiotherapy, which consisted of concurrent systemic administration (n=24), intra-arterial infusion chemotherapy (n=21), or both (n=3). All patients were enrolled in this study after obtaining written informed consent prior to treatment in accordance with the guidelines of the institutional review board. Patients were followed-up every month during the first 6 months and every 3-6 months thereafter. The median follow-up period was 27 months (range, 6-50 months). Acute and late toxicities were scored according to the Common Terminology Criteria of Adverse Events, version 3.0.

Statistical analysis. All statistical analyses were performed using the Stat-view 5.0 statistical software (SAS Institute, Inc., Cary, NC, USA). Frequencies were analyzed using the χ^2 test. Means were compared using the Student's *t*-test for normally distributed data or the Mann–Whitney *U*-test for skewed data. Survival data and cumulative incidences were estimated by the Kaplan–Meier method and examined for significance using the log-rank test. The

Table II. *Analysis of prognostic factors in organ preservation therapy.*

			Initial rsponse				At 3 years				
Variable	Strata	n	Complete response		Other	*p*-Value	PFS	OS	LC	LP	*p*-Value
Age, years	68 or more	22	18	(82%)	4	NS	46%	49%	53%	77%	
	<68	26	20	(77%)	6		55%	61%	59%	77%	0.6
Gender	Male	42	31	(74%)	11	NS	33%	49%	50%	77%	0.69
	Female	6	6	(100%)	0		54%	100%	57%	50%	
T Category	3	25	22	(88%)	3	0.08	56%	67%	65%	71%	0.24
	4	23	15	(65%)	8		40%	45%	45%	77%	
Hemoglobin level	11.5 g/dl or more	32	25	(78%)	7	NS	60%	*71%	*70%	79%	0.0022
	<11.5 g/dl	16	12	(75%)	4		25%	25%	28%	61%	
Location	Larynx	14	12	(86%)	2	NS	80%	*92%	*86%	*93%	0.0004
	Hypopharynx	19	16	(84%)	3		48%	50%	65%	83%	
	Cervical esophagus	15	9	(60%)	6		¶20%	¶27%	¶20%	¶26%	
N category	0	22	20	(91%)	2	0.07	72%	*95%	*76%	73%	0.0004
	1-	26	17	(65%)	9		29%	28%	40%	74%	
Operability	Yes	33	28	(85%)	5	NS	50%	61%	54%	67%	0.44
	No	15	9	(60%)	6		42%	47%	56%	89%	

PFS: Progression-free survival; OS: overall survival, LC: local control rate, LP; larynx preservation survival rate. *$p<0.01$, #$p<0.05$, ¶ at 32 months.

Cox's proportional hazard model was used for multivariate analysis. All analyses used the conventional $p<0.05$ level of significance.

Results

Six patients did not complete treatment. Tumor progression was observed in two cases (one T3N1 cervical esophageal cancer at 30 Gy and one T3N0 supraglottic cancer at 36 Gy), which required interruption of radiotherapy. Radiotherapy was interrupted in four patients because of toxicity (two at 30 Gy, one at 36 Gy, one at 46 Gy, and two at 52 Gy). Of the 48 enrolled patients, 37 (77%) achieved a complete response (partial response, n=6; no change, n=3; and progressive disease, n=2). Tumor category and nodal involvement showed borderline significance for obtaining complete response. Recurrence was observed in 12 patients that achieved a complete response developed recurrence (local, n=7; nodal, n=2; and both, n=2). Out of these 12 patients, five with local and one with nodal recurrence underwent salvage surgery, while 3 patients with local recurrences and one with nodal recurrence were alive with no evidence of disease so far. In those who did not achieve a complete response, only one with a partial response of supraglottic T4N0 disease did not exhibit disease progression. At present, 29 (60%) patients are alive without any evidence of disease, 1 died of other causes and 1 patient is was alive with recurrent disease. The 2- and 3-year local control (LC), progression-free survival (PFS), OS, and laryngeal preservation (LP) rates were 60% and 56%, 55% and 48%, 66% and 56%, and 78% and 73%, respectively. Tumor location, nodal involvement, and pretreatment serum hemoglobin value were identified as predisposing factors not only for PFS but also LC and OS rates (Table II). Multivariate analysis revealed that pretreatment serum hemoglobin value [$p=0.0408$; 95% confidence interval (CI)=1.0380–5.670; odds ratio (OR)=2.426] and tumor location ($p=0.0089$; 95% CI/OR=0.115-0.883/0.319 for hypopharyngeal cancer and 0.017-0.477/0.089 for laryngeal cancer, respectively) were statistically significant prognostic factors for PFS. PFS at 3 years was achieved in 60% patients with a pre-treatment hemoglobin value of ≥11.5 g/dl, but only in 25% of those with levels of <11.5 g/dl ($p=0.0022$) (Table II, Figure 1A). Patients with laryngeal or hypopharyngeal cancer achieved better PFS than those with cervical esophageal cancer ($p=0.0004$) (Table II) (Figure 1B). Interestingly, nodal invasion was a statistically significant prognostic factor not only for OS and PFS but also LC and was borderline significant for initial response but not LP. Induction chemotherapy was administered to 24 patients. Response to induction chemotherapy was a statistically significant predisposing factor for OS among these 24 patients ($p<0.05$). The 3-year OS rate of one complete response and 16 partial

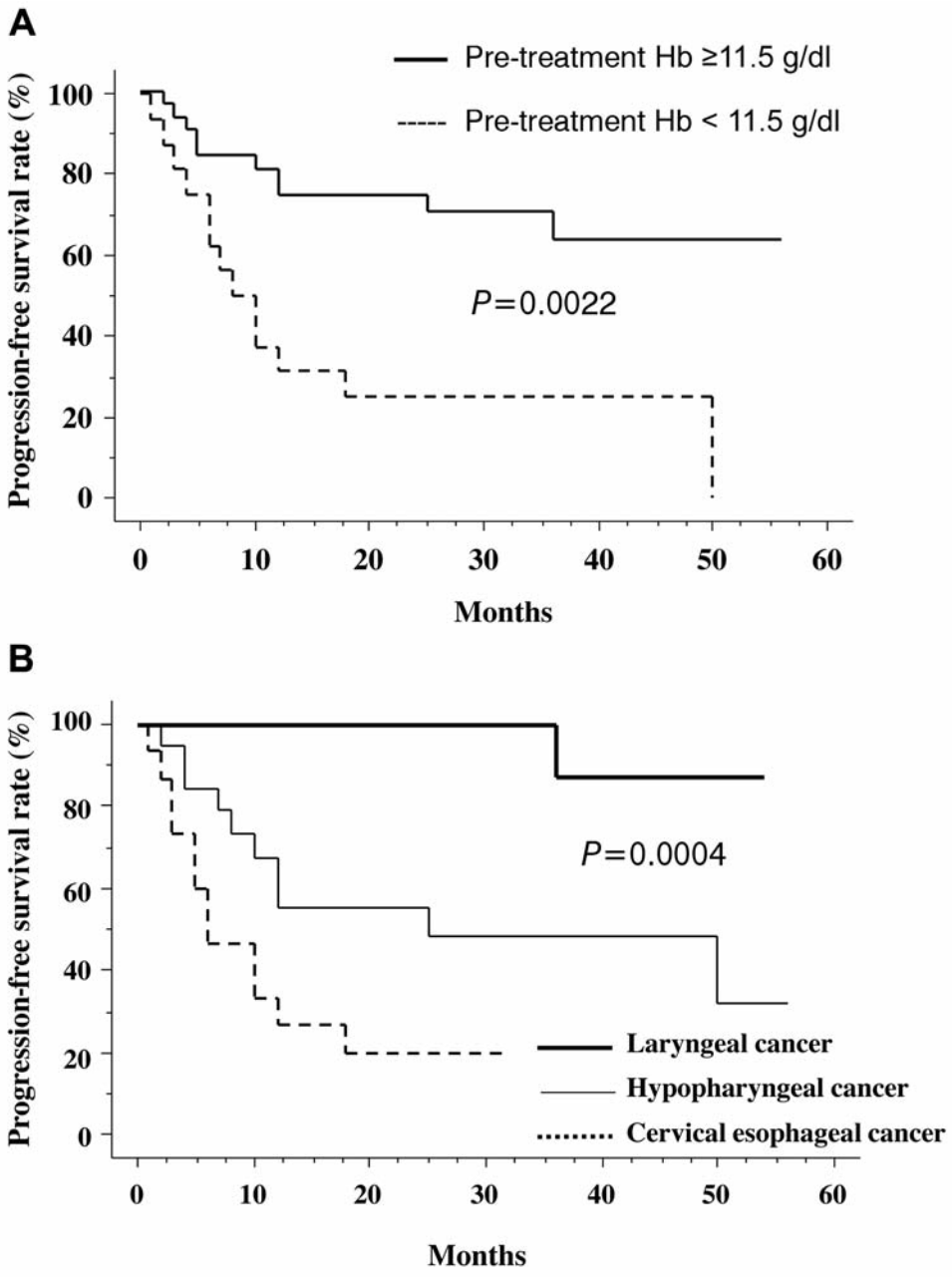

Figure 1. *Influence of hemoglobin level and location of tumors. a) Progression-free survival according to hemoglobin level. Progression-free survival at 3 years for patients with the pretreatment hemoglobin value of ≥11.5 g/dl was 60% (solid line), whereas counterpart showed 25% (dotted line) of progression free survival (p=0.0022). b) Progression-free survival according to location of tumors. Laryngeal cancer showed best progression free survival (solid line, 88% at 3-years), than hypopharyngeal cancer (thin line, 48% at 3-yeras) and cervical esophageal caner (dotted line, 20% at 32 months, p=0.0004).*

response cases was 44% and 17% for poor responders (three with stable disease and one with progressive disease).

Eleven patients experienced 13 episodes of acute ≥grade 3 toxicity (23%, Table III). Of these, RT was interrupted midway of treatment in four patients, all of whom had T4 cervical esophageal cancer (Table III) (esophageal perforation at 46 Gy, lung fistula at 52 Gy, grade 3 pneumonia at 52 Gy, and grade 4 repeated aspiration pneumonia due to bilateral recurrent nerve palsy during induction chemotherapy, which required tracheotomy). Five instances of late toxicity ≥grade 3 occurred in four patients. One patient required gastrostomy for grade 3 dysphasia after

Table III. *Adverse reactions*.

	Grade 3	Grade 4	Grade 5
Acute reaction			
Hematological	5		
Gastrointestinal	2		Esophageal perforation
Respiratory system	3		Lung fistula
Other		1	
Late reaction			
Gastrointestinal	2		
Respiratory system	1		
Other	2		

salvage surgery for lymph node recurrence at 25 months and was alive without any evidence of disease at 48 months. One patient showed continuous grade 3 percutaneous endoscopic gastrostomy dependency without recovery from acute grade 3 toxicity even at 32 months. Two patients exhibited recurrent ipsilateral nerve palsy.

Discussion

To the best of our knowledge, this is the first report to identify predisposing factor for larynx-preservation strategies in patients with grade T3-4 hypopharyngeal, larynx, and cervical esophagus tumors, which would otherwise require laryngectomy. Lefebvre *et al*. (1) reported the results of a randomized phase III study comparing an induction chemotherapy arm with immediate surgery, with or without a postoperative radiotherapy arm in patients with stage II–IV hypopharyngeal cancer. The trial included 194 patients, and the 3- and 5-year OS rates were 57% and 30% for the induction chemotherapy arm group and 43% and 35% for the postoperative RT arm. The 3- and 5-year disease-free survival rates were 43% and 25% for the induction chemotherapy group and 32% and 27% for the postoperative RT arm group, respectively. Hienrmann *et al*. (9) reported 5-year local control rates for stage T3 and T4 glottis cancer of 78% and 81%, and 84% and 87%, respectively, while the OS rates for stage III and IVa disease (American Joint Committee on Cancer guidelines) were 52% and 67%, respectively (9). The actuarial OS rates of cervical esophageal cancer treated by surgery and/or chemotherapy and/or radiotherapy at 2 years are reportedly 24%-47.6% (10, 11). In general, our findings were in accordance with those of previous reports.

Tumor location is a significant prognostic factor for local control, PFS, OS, and LP. Patients with laryngeal and hypopharyngeal cancer achieved better outcomes than those with cervical esophageal cancer, which may be largely dependent on the natural course of these diseases and partly because of the inclination for severe adverse reactions because ≥grade 4 disease was only observed among patients with T4 esophageal cancer. If we exclude these patients from analysis, PFS of cervical esophageal cancer improved from 27% to 27% at 32 months. However, we did not exclude any patients who did not complete the planned treatment schedule because our aim was to identify good candidates for larynx preservation strategies and survey treatment outcome. Our findings demonstrated that tumor location is a strong prognostic factor of nonsurgical modalities to achieve larynx preservation for patients with T3-4 cancer. As a limitation of this study, selection bias may have occurred because we primarily chose intra-arterial infusion chemotherapy for laryngeal cancer based on our previous experience that patients with laryngeal cancer are good treatment candidates, even those with stage T3 and 4 disease (7, 8). However, we did not want to overestimate laryngeal cancer outcomes because we conducted a single-institutional retrospective study; thus, a prospective analysis with a larger number of patients and a longer follow-up period is warranted. Of note, not only OS and PFS, but also local control and larynx-preservation rates, were affected by lymph node involvement in the univariate analysis. Although lymph node involvement is one of the strongest prognostic factors for survival, it is interesting that lymph node status was significantly correlated with local control, implying the importance of nodal involvement when considering approaches for larynx preservation.

Pre-treatment hemoglobin levels have been implicated as indicators of poor treatment outcomes in patients with multiple lesions and cancers of the cervix, head and neck (12), esophagus (13), bladder, breast, and lung (14-15). Becker *et al*. reported a significant correlation between a pretreatment hemoglobin level of ≥12 g/dl and improved OS rate and locoregional control in a multivariate analysis of 153 patients with non-metastatic stage IV squamous cell carcinoma of the head and neck (12). The prognostic value of hemoglobin may be explained by radiobiological data, showing an association between hypoxia with increased resistance of tumor cells to radiotherapy. In addition, tumor oxygenation is affected by the oxygen-carrying capacity of the blood, as represented by the hemoglobin level. Therefore, attempts have been made to improve treatment outcomes of cancer patients with anemia using erythropoietin or red blood cell transfusions. A Cochrane review based on five randomized controlled trials suggested poor locoregional control and PFS and OS rates of patients with head and neck cancers following the addition of erythropoietin to radiotherapy (16). These results suggest that the lack of benefit from erythropoietin therapy may be partly due to the presence of erythropoietin receptors on tumor cell membranes, which stimulate tumor growth or decrease tissue oxygenation because of increased viscosity when hemoglobin concentrations become extremely high (12, 17, 18).

Interestingly, anemia patients showed equivocal initial response if used chemoradiotherapy, however, the prognosis was poor. We speculated that anemia is not only important for radiosensitization but also for tumor re-population after chemoradiotherapy. At present, the results of both prospective and retrospective studies have indicated that the poor prognosis of cancer patients presenting with anemia cannot be improved by a chemoradiotherapy approach (12-19).

In conclusion, pre-treatment hemoglobin levels and tumor locations are important prognostic factors for PFS following multimodal non-surgical organ preservation strategies.

Conflicts of Interest

The Authors declare that they have no competing interests.

References

1 Lefebvre JL, Chevalier D, Luboinski B Kirkpatrick A, Collette L and Sahmoud T: Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst *88*: 890-899, 1996.

2 Pignon JP, Bourhis J, Domenge C and Designé L: Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data—MACH-NC Collaborative Group, Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet *355*: 949-955, 2000.

3 Posner MR, Hershock DM, Blajman CR *et al*: TAX 324 Study Group. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med *357*: 1705-1715, 2007.

4 Pointreau Y, Garaud P, Chapet S *et al*: Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst *101*: 498-506, 2009.

5 Suzuki G, Ogo E, Abe T *et al*: Non-surgical multimodality treatment for locally advanced (T3-4) hypopharyngeal cancer: the impact of pre-treatment hemoglobin level. Anticancer Res *33*: 5561-5565, 2013.

6 Lambert L, Fortin B, Soulières D *et al*: Organ preservation with concurrent chemoradiation for advanced laryngeal cancer: are we succeeding? Int J Radiat Oncol Biol Phys *76*: 398-402, 2010.

7 Tanaka N, Abe T, Uchiyama Y *et al*: Intra-arterial Cehmoradiation for laryngeal and pharyngeal carcinomas: Clinicial Neurovascular anatomy and the hemodynamic balances in head and neck carcinoma. Jpn J Intervent Radiol *24*: 16-24, 2009.

8 Nakashima T, Mihoki T, Ono T, Umeno H and Tanaka N: Selective (intra-arterial), rapid infusion chemo-radiotherapy to preserve the larynx in advanced laryngeal carcinoma: preliminary results. J Laryngol Otol *123(Suppl 31)*: 30-34, 2009.

9 Hinerman RW, Mendenhall WM, Morris CG, Amdur RJ, Werning JW and Villaret DB: T3 and T4 true vocal cord squamous carcinomas treated with external beam irradiation: a single institution's 35-year experience. Am J Clin Oncol *30*: 181-185, 2007.

10 Uno T, Isobe K, Kawakami H, Ueno N, Shimada H, Matsubara H, Okazumi S, Nabeya Y, Shiratori T, Kawata T, Ochiai T and Ito H. Concurrent chemoradiation for patients with squamous cell carcinoma of the cervical esophagus. Diseases of the Esophagus *20*: 12-18, 2007.

11 Mendenhall WM, Sombeck MD, Parsons JT, Kasper ME, Stringer SP and Vogel SB: Management of cervical esophageal carcinoma. Semin Radiat Oncol *4*: 179-191, 1994.

12 Becker A, Stadler P, Lavay RS Hänsgen G, Kuhnt T, Lautenschläger C, Feldmann HJ, Molls M and Dunst J: Severe anemia is associated with poor tumor oxygenation in head and neck squamous cell carcinomas. Int J Radiat Oncol Biol Phys *46*: 459-466, 2000.

13 Zhang F, Han H, Wang C Wang J, Zhang G, Cao F and Cheng Y: A retrospective study: the prognostic value of anemia, smoking and drinking in esophageal squamous cell carcinoma with primary radiotherapy. World J Surg Oncol *11*: 249, 2013.

14 Grau C, Overgaard J. Significance of hemoglobin concentration for treatment outcome. In:Molls M, Vaupel P, editors. Blood perfusion and microenvironment of human tumors. Berlin/Heidelberg/New York: Springer-Verlag; 1998. p. 101-112.

15 Hoff CM, Lassen P, Eriksen JG, Hansen HS, Specht L, Overgaard M, Grau C, Johansen J, Bentzen J, Andersen L, Evensen JF and Overgaard J: Does transfusion improve the outcome for HNSCC patients treated with radiotherapy?—Results from the randomized DAHANCA 5 and 7 trials. Acta Oncol *50*: 1006-1014, 2011.

16 Lambin P, Ramaekers BL, van Mastrigt GA, Van den Ende P, de Jong J, De Ruysscher DK and Pijls-Johannesma M: Erythropoietin as an adjuvant treatment with (chemo) radiation therapy for head and neck cancer (review). Cochrane Database Syst Rev *3*: 1-30, 2009.

17 Vaupel P: Hypoxia and aggressive tumor phenotype: implications for therapy and prognosis. Oncologist *13*: 21-26, 2008.

18 Henke M, Mattern D, Pepe M, Bézay C, Weissenberger C, Werner M and Pajonk F: Do erythropoietin receptors on cancer cells explain unexpected clinical findings? J Clin Oncol *24*: 4708-4713, 2006.

19 Prosnitz RG, Yao B, Farrell CL, Clough R and Brizel DM: Pretreatment anemia is correlated with reduced effectiveness of radiation and concurrent chemotherapy in advanced head and neck cancer. Int J Radiat Oncol Biol Phys *61*: 1087-1095, 2005.

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