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ORIGINAL ARTICLE

Factors influencing the development of distant metastases in patients with head and neck squamous cell carcinoma

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Summary

Purpose: *The aim of this retrospective study was to evaluate the frequency of distant metastases (DM) and to define factors that influence DM free survival (DMFS) in patients with head and neck squamous cell carcinoma (HNSCC).*

Methods: *The charts of 201 patients with oral cavity, pharyngeal, or laryngeal carcinoma, treated with postoperative radiotherapy (RT) or definitive RT between 1999 and 2004 and achieved locoregional control were analyzed.*

Results: *DM occurred in 26 of 201 (12.9%) patients. The mean time of DM diagnosis was 16.5 months (range 5-35). The median time to death after diagnosis of DM was 5 months (range 1-13). The DMFS rate at 5 years was 84.8%. Univariate analysis demonstrated that the risk of DM was significantly influenced by age (p=0.047), cigarette smoking (p=0.024), ECOG performance status (PS) (p=0.008), location of the primary site (p=0.003), N stage (p<0.0001), overall stage (p<0.0001), histological differentiation (p<0.0001), levels of nodal involvement (p<0.0001), treatment modality (p=0.0002), presence of locoregional recurrence (LRR) (p<0.0001), and time to LRR (p<0.0001). In multivariate analysis nodal involvement (N1: p=0.007; N2: p=0.036; N3: p=0.043), and the time to LRR ≤ 6 months (p=0.037) were proven as independent factors that significantly influenced DMFS.*

Conclusion: *Development of DM in patients with HNSCC was significantly influenced by the presence of positive nodal status and the presence of LRR whose appearance was within 6 months of RT.*

Key words: distant metastases, head and neck carcinoma, radiotherapy

Introduction

HNSCCs are frequent tumors diagnosed in more than half a million patients worldwide each year [1]. Approximately two thirds of the patients with HNSCC have advanced disease at presentation. HNSCCs tend to remain localized at the primary site for a period of time and preferentially metastasize to regional lymph nodes rather than to spread to other than regional lymph nodes or to metastasize hematogenously [2-4]. Over the last decades, intensified locoregional treatment modalities including concurrent chemoradiotherapy (CCRT), enabled significant improvement in the locoregional control in patients with advanced HNSCC. However, this improvement does not appear to modify the final outcome of these patients, mainly due to the appearance of DM and second primary tumors [5].

The reported frequency of DM in series based on clinical data has varies extensively, ranging between 4 and 26% [6-15].

The occurrence of DM in patients in whom locoregional control has been already achieved could be considered as a consequence of the existence of subclinical distant metastatic disease at the time when locoregional treatment was carried out. The development of these metastatic foci leads to clinically apparent DM, being a devastating event often characterized by pain, cachexia and death and, in that way, representing one of the most frequent reasons for morbidity and mortality in HNSCC patients in the late follow-up period [14-16].

The purpose of this retrospective study was to analyze the frequency of clinically manifested DM in patients with HNSCC treated with postoperative RT or RT alone in whom treatment achieved locoregional

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control, and also to determine the role of several prognostic factors in predicting the development of DM. Providing potential prognostic factors it could be possible to better identify subgroups of patients who are at greatest risk for DM and select them for therapeutic strategies designed to treat occult metastatic disease.

Methods

The records of patients with biopsy-proven HNSCC who were managed with curative intent at the University Clinic of Radiotherapy and Oncology in Skopje between February 1999 and June 2004 were analyzed. All patients had undergone pretreatment evaluation of clinical disease stage (primary, regional, and distant sites) including medical history, physical examination, complete blood count and routine blood biochemistry, computed tomography (CT) or magnetic resonance imaging (MRI) scans of the head and neck, chest x-ray, and liver ultrasound. Patients who had metastatic disease at presentation were excluded from the study. The time to the appearance of DM after the date of commencement of RT was calculated in each patient. DMFS was measured from the start of treatment to the date of the occurrence of clinically detected DM or the date of last patient's visit.

Patient characteristics

A total of 201 patients were included in the study, 172 males and 29 females. Median age was 57 years (range 34-79). Only 5% (10/201) of the patients were nonsmokers. Without evidence of alcohol consumption were 62 (30.9%) patients. Detailed patient characteristics are shown in Table 1.

Tumor characteristics

The most frequent site of the primary tumor was the larynx (100/201; 49.8%). The tumor stage was determined according to 1997 International Union Against Cancer and American Joint Committee of Cancer (UICC and AJCC) TNM classification criteria [17]. There were only 6 patients with T1 lesion while more than one half of the patients had T3-T4 primary lesion. No evidence of nodal disease in the neck (N0) was present in 59.7% of the patients (120/201). The tumors were well differentiated in 40.8% of the cases, moderately differentiated in 31.8%, undifferentiated in 14.4%, and in the remaining cases the degree of differentiation was unknown. Detailed tumor characteristics are listed in Table 2.

Table 1. Patient characteristics (n= 201)

Characteristics	*No. of patients (%)*
Gender	
Male	172 (85.6)
Female	29 (14.4)
Age (years)	
< 40	11(5.5)
40-60	116 (57.7)
> 60	74 (36.8)
Cigarette smoking (no./day)	
No	10 (5.0)
≤ 20	99 (49.2)
> 20	92 (45.8)
Alcohol consumption (g/day)	
No	62 (30.9)
≤ 200	106 (52.7)
> 200	33 (16.4)
ECOG PS	
0	167 (83.1)
1	34 (16.9)

Table 2. Tumor characteristics (n= 201)

Characteristics	*No. of patients (%)*
Location	
Oral cavity	32 (15.9)
Oropharynx	35 (17.4)
Hypopharynx	34 (16.9)
Larynx	100 (49.8)
T stage	
T1	6 (3.0)
T2	72 (35.8)
T3	87 (43.3)
T4	36 (17.9)
N stage	
N0	120 (59.7)
N1	43 (21.4)
N2	35 (17.4)
N3	3 (1.5)
Overall stage	
I	3 (1.5)
II	44 (21.9)
III	80 (39.8)
IV	74 (36.8)
Histological differentiation	
Good	82 (40.8)
Moderate	64 (31.8)
Poor	29 (14.4)
NOS	26 (13.0)
Levels of positive nodes	
None	120 (59.7)
High (I and II)	62 (30.8)
Low (III-V)	19 (9.5)

NOS: not otherwise specified

Treatment and follow-up

Patients were treated with either postoperative RT

or RT alone. RT was given as adjuvant treatment following surgery to 117 (58.2%) patients. RT as definitive treatment option was administered to 84 (49.8%) patients. RT was delivered utilizing telecobalt therapy (TCT) unit with a conventional fractionation schedule and a dose of 60-70 Gy in 6-7 weeks (one fraction of 2 Gy per day, 5 fractions per week).

The first assessment of tumor response in patients treated with RT alone was performed 3 months after completion of treatment by physical examination, fiberoptic endoscopy, repeat imaging studies, and repeat endoscopy and biopsy. Patients with locally and/or regionally persistent disease were excluded from the analysis.

Patients were followed at regular intervals for at least 5 years. Follow-up consisted of physical examination and chest x-ray. Other investigations, such as abdominal ultrasound, CT or MRI scan, bone scintigraphy, or brain scans, were performed when clinically indicated. Median follow-up was 42 months (range 5-124).

Locoregional recurrences

Among the 201 patients 73 (36.3%) developed LRR as the first site of failure. Of those, 20 patients had their recurrence above the clavicles, manifested within 6 months from the beginning of RT.

Analyzed prognostic variables

The following variables were evaluated in relation to DM: age at onset (< 40 years vs. 40-60 vs. > 40 years), gender, cigarette smoking, alcohol consumption, ECOG PS, location of the primary site (oral cavity vs. oropharynx vs. hypopharynx vs. larynx, T stage (T1 vs. T2 vs. T3 vs. T4), N stage (N0 vs. N1 vs. N2 vs. N3), overall stage (I vs. II vs. III vs. IV), histological differentiation (good vs. moderate vs. poor), levels of nodal involvement (none vs. high levels [I and II] vs. low levels [III-V]), treatment modality (postoperative RT vs. RT alone), presence of LRR, and time to LRR.

Statistical analysis

Univariate and multivariate analysis were carried out to determine the relative role of these variables in the subsequent development of DM. All variables were evaluated by univariate analysis to assess their effect on DMFS. DMFS has been estimated as a function of time by Kaplan-Meier method. The significance of the relation of certain factors with DMFS was tested by log-rank test and p-value. The Cox's regression model-method Forward LR was used to reveal the significance and independence of each prognostic factor. Statistical significance was defined as p-value less than 0.05.

Results

DM developed in 26 (12.9%) patients. In 18 of them the identification of metastatic disease was preceded by the occurrence of LRR. The remaining 8 patients developed DM without evidence of LRR. The sites of DM were distributed as follows: lung, 18 cases (69.2%); bone, 1 case (3.9%); liver, 3 cases (11.5%); and more than one site, 4 cases (15.4%).

The mean time to occurrence of DM was 16.5 months (SD 7.5; range 5-35); 100% of distant metastatic disease occurred within 30 months after the commencement of treatment (2.5 years; Figure 1).

The median time to death after diagnosis of DM was 5 months (range 1-13); 96% of patients with DM died within 12 months. The median duration of DMFS was 42 months (range 5-124). The DMFS rate at 5 years was 84.8%.

Univariate analysis

Univariate analysis revealed that the following factors significantly influenced DMFS: age, cigarette smoking, ECOG PS, location of the primary site, N stage, overall stage, histological differentiation, levels of nodal involvement, treatment modality, presence of LRR, and time to LRR (Table 3).

Patient factors: Patients' age less than 40 years had a significant negative influence on DMFS compared with the age of 40-60 years and the age of more than 60 years (p=0.047). Cigarette smoking and ECOG PS 1 also influenced negatively DMFS (p=0.024 and p=0.008, respectively).

Tumor factors: Patients with oropharyngeal or hypopharyngeal primary lesions had worse prognosis related to DMFS compared with the group of patients with

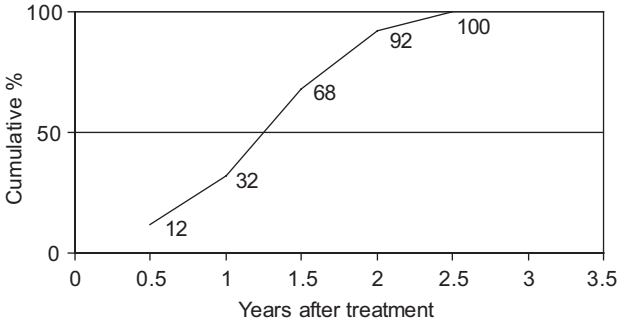

Figure 1. Proportion of total number of patients with distant metastases.

Table 3. Univariate analysis of distant metastases-free survival

Factor	*No. of patients*	*Median DMFS (months)*	*5-year DMFS (%)*	*p-value*
Gender				n.s.
Male	172	38	84.7	
Female	29	53	85.8	
Age (years)				0.047
< 40	11	17	60.2	
40-60	116	43	83.7	
> 60	74	44.5	90.1	
Cigarette smoking (no. per day)				0.024
No	10	57.5	100.0	
≤ 20	99	33	76.7	
> 20	92	49	91.3	
Alcohol consumption (g/day)				n.s.
No	62	50	90.2	
≤ 200	106	45.5	83.3	
> 200	33	23	73.7	
ECOG PS				0.008
0	167	47	86.6	
1	34	20	70.7	
Location				0.003
Oral cavity	32	28	84.6	
Oropharynx	35	34	76.6	
Hypopharynx	34	34	67.3	
Larynx	100	49	93.8	
T stage				n.s.
T1	6	63	100.0	
T2	72	54.5	85.8	
T3	87	33	84.8	
T4	36	22.5	79.2	
N stage				<0.0001
N0	120	53.5	94.7	
N1	43	31	78.7	
N2	35	17	47.7	
N3	3	7	0	
Overall stage				<0.0001
I	3	72	100.0	
II	44	62.5	97.3	
III	80	45.5	90.2	
IV	74	19.5	65.3	
Histological differentiation				<0.0001
Good	82	53.5	93.2	
Moderate	64	47.5	91.2	
Poor	29	18	48.3	
NOS	26	24.5	66.3	
Levels of positive nodes				<0.0001
None	120	53.5	94.7	
High (I and II)	62	28	75.4	
Low (III-V)	19	15	0	
Treatment				0.0002
Postoperative RT	117	49	92.7	
RT alone	84	28	71.8	
LRR				<0.0001
Yes	73	17	0	
No	128	57	93.7	
Time to LRR (months)				<0.0001
No LRR	128	57	93.7	
> 6	53	20	61.2	
≤ 6	20	10	0	

DMFS: distant metastases-free survival, n.s.: not significant, NOS: not otherwise specified, LRR: locoregional recurrence, RT: radiotherapy

primary tumors originating from the oral cavity and the larynx (p=0.003). Patients with nodal involvement had significantly worse prognosis compared with patients without evidence of nodal disease in the neck (N0) (p<0.0001). Overall stage IV had a significant negative influence on DMFS compared with overall stages I, II and III (p<0.0001). The degree of differentiation was identified as statistically significant factor for duration of DMFS (p<0.0001). The most unfavorable influence on DMFS had tumors with poor histological differentiation. Low level positive nodes of the neck had highly unfavorable influence on DMFS (p<0.0001).

Treatment and outcome factors: The group of patients treated with RT alone had worse prognosis in relation with DMFS compared with the group treated with postoperative RT (p=0.0002). The presence of LRR had a significant negative impact on DMFS. Patients who developed LRR had significantly worse prognosis related to DMFS compared with patients who had continuous control above the clavicles (p<0.0001). The time to LRR was identified as a significant unfavorable prognostic factor for DMFS. Patient with time to LRR ≤ 6 months had significantly worse prognosis in terms of DMFS (p<0.0001).

Multivariate analysis

Multivariate analysis revealed that N stage (N1 vs. N0: HR=6.18, 95% CI 1.65 - 23.09, p=0.007; N2 vs. N0: HR=4.89, 95% CI 1.11 - 21.47, p=0.036; and N3 vs. N0: HR=10.20, 95% CI 1.07 - 97.22, p=0.043), and the time interval between treatment and LRR ≤ 6 months (HR=5.22, 95% CI 1.10 - 24.72, p=0.037) were independent factors that significantly influenced DMFS (Table 4).

The 5-year DMFS for the subset of patients who presented with N0 neck disease was 94.7%, compared with 78.7%, 47.7%, and 0% for patients with N1, N2 and N3 neck disease, respectively (p<0.0001; Figure 2).

Table 4. Multivariate analysis of distant metastases-free survival

Factor	*HR*	*95% CI*	*p-value*
N stage			
N1 vs. N0	6.18	1.65 - 23.09	0.007
N2 vs. N0	4.89	1.11 - 21.47	0.036
N3 vs. N0	10.20	1.07 - 97.22	0.043
Time interval between treatment and LRR (months)			
≤ 6 vs. > 6	5.22	1.10 - 24.72	0.037

HR: hazard ratio, 95% CI: 95% confidence interval, LRR: locoregional recurrence

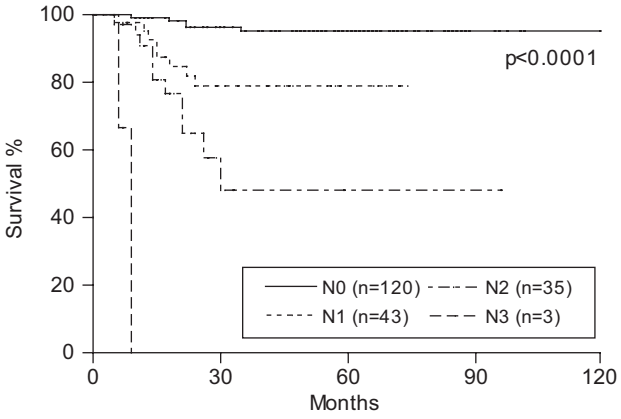

Figure 2. Kaplan-Meier curves of distant metastases-free survival by N stage.

Discussion

The appearance of DM in a substantial period after the completion of the initial treatment represents a factor that seriously limits survival of patients with HNSCC.

In our study the incidence of DM was 12.9%, which corresponds with the frequency of DM observed in other clinical studies. In the series of 281 patients with HNC, Leemans et al. [12] reported that DM were demonstrated in 26 (9.3%) patients. Retrospectively reviewing 2,550 patients with squamous cell carcinoma of the larynx and hypopharynx, Spector [4] found an overall incidence of DM of 8.5%. In the retrospective study carried out on 5,019 patients with previously untreated HNSCC, Merino et al. [7] revealed an incidence of DM of 10.9%. On the other hand, the overall incidence of DM of 25.1% reported by Papac [18], and the frequency of DM as first site of failure of 23% reported by Alvi and Johnson [14] are twice as many compared to the incidence of DM revealed in our study.

According to the data from the literature, the most common sites of DM are lung, bones and liver [2,13, 19-24]. In our study, lungs were the most frequent site of DM (69.2%).

The mean time to occurrence of DM in our study was 16.5 months. In the study of Caballero et al. [21], the average interval between surgery and DM development was 19.1 months, while in the study of Hsu and Chen [19], the median interval between the diagnosis and the occurrence of DM was 8 months. Leon et al. [15] reported that 85% of DM were diagnosed within the first 2 years of follow-up. Similar data were reported by Caballero et al. [21] with 75% of DM occurring within the first 2 years following treatment. In our study, 100% of distant metastatic disease occurred within 2.5 years of treatment. According to Buckley [25], the oc-

currence of DM 3 years after treatment should be considered as unusual.

Although there are different factors recognized to be involved in the development of DM, a general agreement exists over the striking impact of the N stage on the presence or absence of DM [7,11,12,15,18,21,26,27]. In our study, nodal involvement was the only prognostic factor related to tumor characteristics identified as significant independent determinant for DMFS. The levels of positive nodes did not appear to independently correlate with DMFS in the regression analysis.

In the study of Al-Othman et al. [28] carried out on 873 patients treated with definitive RT, N stage was also identified as a prognostic factor that had great influence on DMFS. Hsu and Chen [19] evaluating possible risk factors for DM in 735 patients with HNSCC also found N classification being one of the significant risk factors for DM. On the contrary, in the retrospective study on 832 HNC patients carried out by Kotwall et al. [29], patients with N2 and N3 neck metastases were not at higher risk for developing DM than patients with N0 necks.

Analyzing the development of DM from the standpoint of locoregional disease control it can be realized that many authors have found LRR being a factor markedly associated with an increased probability of developing DM [7,15,16,19]. In the series of Caballero et al. [21], local and regional recurrence were shown as associated with a higher percentage of DM. According to Leibel et al. [26], locoregional control was a significant independent prognostic factor related to the development of DM. These authors pointed out that the achievement of locoregional disease control could be considered as having the greatest impact on distant metastatic spread. In the retrospective analysis of Garavello et al. [27], patients who achieved locoregional control were found to have a lower risk of DM. Al-Othman et al. [28] revealed that continuous control above the clavicles and time to LRR were parameters that significantly influenced DMFS in the univariate analysis. In the multivariate analysis, continuous locoregional control significantly influenced DMFS, while time to locoregional recurrence was not found to be an independent prognostic factor that influenced DMFS.

In our study, univariate analysis revealed that the presence of LRR and time to LRR were factors significantly influencing DMFS. However, in the multivariate analysis, only the time interval between treatment and LRR was found to be an independent factor that significantly influenced DMFS.

Eradication of subclinical distant metastatic disease that leads to decreased frequency of DM is crucial for improvement of survival, especially in patients with nodal disease [15,20]. Although locoregional control seems to have reached a plateau with the increased use of CCRT for advanced stage HNSCC, the development of DM as a pattern of failure in this patient category still remains a problem to be dealt with [20,30]. CCRT as a standard of care for patients with advanced HNSCC aged less than 70 years and when they are candidates for chemotherapy, contributes to improved survival and organ preservation, but has not demonstrated systemic effect to suppress the development of DM. On the other hand, increased locoregional treatment intensity led to an increased risk of distant metastatic disease. Two years after treatment DM occur in approximately 20% of patients with locally advanced disease who are treated with CCRT [1]. The metastatic rate of 20% in two phase 3 studies [31,32], conducted to evaluate the role of postoperative CCRT in high risk HNSCC, also showed that adding cisplatin had no significant effect on the incidence of DM.

The recognition that improvement in locoregional control with aggressive concurrent treatment approaches results in a relative risk of DM suggests that the pattern of treatment failure may be shifting from LRR to distant metastatic disease [33,34]. In this regard, it is reasonable to expect that the use of both induction chemotherapy (IC) and CCRT in a sequential manner may provide optimal benefit for patients with locoregionally advanced HNSCCs since the intervention with IC is directed at improving distant control which might be important in improving overall treatment outcome [1,35].

The data from our study revealed that patients presenting with nodal disease have the greatest risk of having subclinical distant metastatic disease. The presence of LRR and the time interval to LRR were also strongly associated with the development of DM. At this point, it has to be mentioned that although all of the patients included in our study were treated with RT performed with TCT unit, from 2005 on the therapeutic approach to patients with HNC at the University Clinic of Radiotherapy and Oncology in Skopje has been markedly changed due to several reasons. The first, and most important reason, is the installation of new equipment in 2004, which gave us an opportunity to implement three-dimensional conformal RT (3D CRT) as a technique directed toward increased rate of locoregional control. The second reason is that, since 2006, following the recommendations of evidence-based medicine, we have adopted CCRT as a treatment of choice for all of the patients with advanced HNSCC who were candidates for chemotherapy. Considering that both 3DCRT and CCRT are treatment approaches designed to increase locoregional control, we realize that in order to further improve outcomes of patients with locoregionally advanced HNSCC, a neces-

sity exists for intensive treatment strategy in which the addition of IC to CCRT would be potentially able to decrease the frequency of DM. In our opinion, sequential therapy should be considered as a promising treatment option in patients with advanced HNSCC, especially in those with advanced nodal disease.

Introducing new target therapies (e.g. cetuximab) in combination with new advanced RT techniques (Intensity-Modulated Radiation Therapy, Volumetric Modulated Arc Therapy) [36,37] and designing institutional and national-based guidelines for the treatment of patients with advanced stage HNSCC it is expected that the results of the locoregional treatment of this disease would be improved, which would finally result in reduced rate of DM and on the other hand would prolong the overall patient survival.

However, we must emphasize that until the completion of ongoing randomized phase 3 studies comparing sequential therapy with CCRT [1,38,39], the treatment options for patients with advanced high-risk HNSCC still remain to be: postoperative CCRT, CCRT, or IC followed by RT i.e. sequential chemoradiotherapy.

References

1. Haddad RI, Shin DM. Recent advances in head and neck cancer. N Engl J Med 2008; 359: 1143-1154.
2. de Bree R, Deurloo EE, Snow GB, Leemans CR. Screening for distant metastases in patients with head and neck cancer. Laryngoscope 2000; 110: 397-401.
3. Senft A, de Bree R, Hoekstra OS et al. Screening for distant metastases in head and neck cancer patients by chest CT or whole body FDG-PET: A prospective multicenter trial. Radiother Oncol 2008; 87: 221-229.
4. Spector GJ. Distant metastases from laryngeal and hypopharyngeal cancer. ORL 2001; 63: 224-228.
5. Leon X, Quer M, Diesz S, Orus C, Lopez-Pousa A, Burgues J. Second neoplasm in patients with head and neck cancer. Head Neck 1999; 21: 204-210.
6. O'Brien PH, Carlson R, Steubner EA Jr, Staley CT. Distant metastases in epidermoid cell carcinoma of the head and neck. Cancer 1971; 27: 304-307.
7. Merino OR, Lindberg RD, Fletcher GH. An analysis of distant metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1977; 40: 145-151.
8. Dennington ML, Carter DR, Meyers AD. Distant metastases in head and neck epidermoid carcinoma. Laryngoscope 1980; 90: 196-201.
9. Vikram B, Strong E, Shah J, Spiro R. Failure at distant sites following multimodality treatment for advanced head and neck cancer. Head Neck 1984; 6: 730-733.
10. Hong WK, Bromer RH, Amato DA et al. Patterns of relapse in locally advanced head and neck patients who achieved complete remission after combined modality therapy. Cancer 1985; 56: 1242-1245.
11. Zbaren P, Lehman W. Frequency and sites of distant metastases in head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck Surg 1987; 113: 762-764.
12. Leemans CR, Tiwari R, Nauta JJP, van der Waal I, Snow GB. Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. Cancer 1993; 71: 452-456.
13. Troell RJ, Terris DJ. Detection of metastases from head and neck cancers. Laryngoscope 1995; 105: 247-250.
14. Alvi A, Johnson JT. Development of distant metastasis after treatment of advanced-stage head and neck cancer. Head Neck 1997; 19: 500-505.
15. Leon X, Quer M, Orus C, del Prado Venegas M, Lopez M. Distant metastasis in head and neck cancer patients who achieved loco-regional control. Head Neck 2000; 22: 680-686.
16. Spector GJ, Sessions DG, Haughey BH et al. Delayed regional metastases, distant metastases, and second primary malignancies in squamous cell carcinomas of the larynx and hypopharynx. Laryngoscope 2001; 111: 1079-1087.
17. International Union Against Cancer (UICC). TNM classification of malignant tumors (5th Edn). In: Sobin LH, Wittekind CH (Eds). New York (NY): Wiley-Liss,1997.
18. Papac RJ. Distant metastases from head and neck cancer. Cancer 1984; 53: 342-345.
19. Hsu L-P, Chen P-R. Distant metastases of head and neck squamous cell carcinomas-experience from Eastern Taiwan. Tzu Chi Med J 2005; 17: 99-104.
20. Shingaki S, Takada M, Sasai K et al. Impact of lymph node metastasis on the pattern of failure and survival in oral carcinoma. Am J Surg 2003; 185: 278-284.
21. Caballero M, Vilaseca I, Bernal-Sprekelsen M, Guilemany JM, Moragas M, Blanch JL. Distant metastases after transoral laser microsurgery for laryngeal and hypopharyngeal squamous cell carcinoma. Head Neck 2008; 30: 1599-1606.
22. Jackel MC, Rausch H. Distant metastases from squamous-cell carcinomas of the upper aerodigestive tract. The influence of clinical tumor parameters and the course of the disease. HNO 1999; 47: 38-44.
23. Calhoun KH, Fulmer P, Weiss R, Hokanson JA. Distant metastases from head and neck squamous cell carcinomas. Laryngoscope 1994; 104: 1199-1205.
24. Ferlito A, Shaha AR, Silver CE, Rinaldo A, Mondin V. Incidence and sites of distant metastases from head and neck cancer. ORL J Otorhinolaryngol Relat Spec 2001; 63: 202-207.
25. Buckley JG. The future of head and neck surgery. J Laryngol Otol 2000; 114: 327-330.
26. Leibel SA, Scott CB, Mohiuddin M et al. The effect of local-regional control on distant metastatic dissemination in carcinoma of the head and neck: results of an analysis from RTOG head and neck database. Int J Radiat Oncol Biol Phys 1991; 21: 549-556.
27. Garavello W, Ciardo A, Spreafico R, Gaini RM. Risk factors for distant metastases in head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck Surg 2006; 132: 762-766.
28. Al-Othman MOF, Morris CG, Hinerman RW, Amdur RJ, Mendenhall WM. Distant metastases after definitive radiotherapy for squamous cell carcinoma of the head and neck. Head Neck 2003; 25: 629-633.
29. Kotwall C, Sako K, Razack MS, Rao U, Bakamjian V, Shedd DP. Metastatic pattern in squamous cell cancer of the head and neck. Am J Surg 1987; 154: 439-442.
30. Taneja C, Allen H, Koness RJ, Radie-Keane K, Wanebo HJ. Changing patterns of failure of head and neck cancer. Arch

Otolaryngol Head Neck Surg 2002; 128: 324-327.
31. Bernier J, Domenge C, Ozsahin M et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004; 350: 1945-1952.
32. Cooper JS, Pajak TF, Forastiere AA et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004; 350: 1937-1944.
33. Vokes EE, Kies MS, Haraf DJ et al. Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer. J Clin Oncol 2000; 18: 1652-1661.
34. Adelstein DJ, Saxton JP, Lavertu P et al. Maximizing local control and organ preservation in stage IV squamous cell head and neck cancer with hyperfractionated radiation and concurrent chemotherapy. J Clin Oncol 2002; 20: 1405-1410.
35. Vokes EE, Kies M, Haraf DJ et al. Induction chemotherapy followed by concomitant chemoradiotherapy for advanced head and neck cancer: impact on the natural history of the disease. J Clin Oncol 1995; 13: 876-883.
36. Bonner JA, Harari PM, Giralt J et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006; 354: 567-578.
37. Bonner JA, Harari PM, Giralt J et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010; 11: 21-28.
38. Adelstein DJ, LeBlanc M. Does induction chemotherapy have a role in the management of locoregionally advanced squamous cell HNC? J Clin Oncol 2006; 24: 2624-2628.
39. Posner MR. Paradigm shift in the treatment of HNC: the role of neoadjuvant chemotherapy. The Oncologist 2005; 10 (Suppl 3): S11-19.