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ORIGINAL ARTICLE

Prognostic factors in patients with recurrent head and neck cancer treated with reirradiation

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Summary

Purpose: *The aim of this study was to determine the prognostic factors concerning overall survival (OS) and progression-free survival (PFS) following reirradiation in patients with recurrent squamous cell head and neck cancer (HNC).*

Patients and methods: *We performed a retrospective analysis on 65 recurrent HNC patients treated with reirradiation for local/locoregional recurrence between 1999 and 2004 at the Institute of Radiotherapy and Oncology in Skopje. The initial treatment of their HNC consisted of radiotherapy following surgery, radiotherapy alone, or concurrent chemoradiotherapy.*

Results: *The median reirradiation dose was 39.8 Gy (range 24-58). Clinically complete response (CR) was observed in 9 (13.9%) patients. The median OS and PFS was 8 months (range 1-22) and 4.9 months (range 0-18), respectively. The univariate analysis of prognostic factors identified Karnofsky performance status (KPS), response to reirradiation, dose to recurrent site, and disease-free interval (DFI) as strongly associated with both OS and PFS. Initial tumor site and cumulative dose had a significant influence only on OS. Multivariate analysis revealed that response to reirradiation and the radiation dose to the recurrent site were two independent variables significantly influencing OS ($p < 0.0001$ and $p = 0.049$, respectively). The only significant independent prognostic factor for PFS was response to reirradiation ($p = 0.0008$).*

Conclusion: *The necessity of improvement of patients' outcome allows us to consider concurrent chemoradiotherapy as a more efficient treatment strategy that has a potential to increase the response to reirradiation of unresectable recurrent HNC. Using higher radiation doses is also expected to enhance the response rates and consequently to positively influence OS and PFS.*

Key words: head and neck cancer, prognostic factors, reirradiation

Introduction

The management of early stage I-II HNC consists of either conservative surgery or definitive radiotherapy resulting in equivalent locoregional control probabilities. Standard therapy for advanced HNC is a combined modality approach using surgery and postoperative radiotherapy with or without chemotherapy, or definitive radiotherapy administered daily, twice daily, or as concomitant boost regimen concurrent with platinum-based chemotherapy. New treatment policies like dose escalation by means of intensity-modulated radiotherapy (IMRT), but also the combination of radiotherapy with molecular targeted agents such as the epidermal growth factor receptor (EGFR) antagonist have recently shown to enhance the effects of radiotherapy [1,2].

Nevertheless, locoregional control in patients with locally advanced tumors remains unsatisfactory, with 3-year rates rarely exceeding 50-60% [3]. Irrespective of the treatment approach initially applied and despite the advances made in the treatment of patients with locally advanced squamous cell HNC, the most frequent treatment failures occur at locoregional sites

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[4-6]. Data from large series and multi-institutional trials indicates wide variation in the rate of local and regional failure-between 20 and 57% [7]. Locoregional recurrences of squamous cell carcinoma of the head and neck that develop despite appropriate and aggressive therapy also appear to increase the development of distant metastases. The incidence of distant metastases detected between 6 months to 2.5 years after treatment are significantly increased in patients who developed locoregional failure within this time period compared to those who remained locally controlled [8]. Therefore, the achievement of locoregional control has greatest importance in achieving improved disease-free (DFS) and OS [7]. The prognosis of patients experiencing recurrent HNC following definitive therapy (surgery/RT/combination of both) is poor with reported median survival of approximately 7 months [9], and with a median survival of 3 months, if the tumor is left untreated [10].

Surgical resection of recurrent squamous cell HNC is the treatment of choice. Unfortunately, the vast majority of recurrent tumors appear unsuitable for surgical intervention because of their unresectability mostly due to the presence of direct extension into the neck including encasement of the carotid artery. Additionally, there is also a proportion of recurrences that, although technically resectable, they cannot be resected because of patient comorbidities or patient refusal.

For patients with recurrent, inoperable HNC chemotherapy is often the treatment of last resort. Unfortunately, no chemotherapy regimen has convincingly demonstrated to prolong survival [4]. Considering patients with recurrent disease being generally incurable, chemotherapy aims at prolonging OS or PFS, and also at improving the quality of life by controlling existing symptoms and preventing new cancer-related symptoms. Consequently, the radiation oncologist is often faced with the challenge of reirradiation. Reirradiation, with or without chemotherapy, appears to be the treatment with the greater potential for cure, but there is always a necessity for delivering high doses of radiation to achieve adequate local tumor control or possible cure. Thus, administration of a second course of radiation to tissues within a previous radiation portal is difficult to perform because of the anticipated high percentage of serious acute and late effects [11].

The aim of this study was to analyze outcomes and factors possibly influencing prognosis for patients with recurrent HNC treated with external beam reirradiation in order to assess the value of this treatment approach. Providing potential prognostic factors we could better tailor therapeutic measures according to the prognosis in order to select patients for intensified protocols i.e. reirradiation with concurrent chemotherapy which is expected to demonstrate substantial toxicity but also has a potential to increase rates of locoregional disease control and survival.

Patients and methods

We have retrospectively reviewed 65 patients with recurrent HNC treated at the Institute of Radiotherapy and Oncology in Skopje between October 1999 and June 2004. The inclusion criteria for this analysis were: a) biopsy-proven recurrence of squamous cell carcinoma in a previously irradiated area of the head and neck; b) initial course of postoperative or definitive radiotherapy being fully completed; c) no major late normal tissue reactions from previous radiation; d) KPS ≥70% [12]; e) inability to carry out locoregional salvage surgery; f) no second primary cancer; g) no evidence of distant metastatic dissemination; h) and reirradiation alone being the retreatment modality of the recurrent tumor.

According to our follow-up policy, after the initial treatment, all patients were followed by surgeons and radiation oncologists. The patients were seen for clinical examination monthly during the first year after they had completed their treatment, every other month in the second year, every 4 months in the third year, every 6 months in the fourth and fifth year, and annually thereafter. Tumor biopsies to obtain histological proof of recurrent primary tumor, and/or fine-needle biopsies to obtain cytological proof of nodal recurrence were performed when there was clinically suspected regrowth of the tumor. Head and neck computed tomography (CT) was obligatory pretreatment examination. The local extent of the disease was also assessed by endoscopy and bimanual palpation.

Patient and tumor characteristics

Of 65 patients included in the study 60 were males and 5 were females. Median age was 54.9 years (range 30-76). The tumors were staged according to International Union Against Cancer and American Joint Committee of Cancer (UICC and AJCC) criteria from 1997 [13]. No T1 lesion was recorded, and almost half of the patients initially had T3 primary lesion. No evidence of nodal disease in the neck (N0) was present in 38.5% (25/65) of the patients. Detailed patient and tumor characteristics prior to initial treatment are shown in Table 1.

Primary tumor treatment

The initial treatment included radiotherapy in all 65 patients. Initial radiotherapy was given as adjuvant

Table 1. Baseline patient and tumor characteristics (total patients = 65)

Characteristic	*Patients* *n*	*%*
Median age (years)	54.9	
Range	30-76	
Gender		
Male	60	92.3
Female	5	7.7
Initial tumor site		
Oral cavity	13	20.0
Oropharynx	8	12.3
Hypopharynx	7	10.8
Larynx	24	36.9
Nasopharynx	11	16.9
Nasal cavity and paranasal sinuses	2	3.1
Initial T stage		
T2	13	20.0
T3	31	47.7
T4	21	32.3
Initial N stage		
N0	25	38.5
N1	18	27.7
N2	19	29.2
N3	3	4.6

treatment following surgery to 32 (49.2%) patients, as definitive treatment to 22 (33.9%) patients, and concurrent with chemotherapy to 11 (16.9%) patients. The concurrent chemoradiotherapy regimen included the administration of low-dose cisplatin (30 mg/m^2 weekly) concurrently with radiation. This treatment was administered to 9 patients with nasopharyngeal cancer and to 2 patients with primary oropharyngeal carcinoma.

Recurrence characteristics

Recurrence at the primary site was present in 17 (26.2%) patients, cervical lymph node recurrence in 27 (41.5%) patients, and simultaneous local and nodal recurrence in 21 (32.3%) patients. DFI was defined as the time from the completion of the initial radiotherapy to diagnosis of recurrence. Median DFI was 13.7 months (range 2-49). At the beginning of reirradiation 36 (55.4%) patients had KPS 70-80% and 29 (44.6%) patients 90-100%.

Treatment of recurrence

Radiotherapy of the recurrences was delivered with photon energy of 1.25 MV using cobalt-60 machine with a source-to-surface or source-to-isocenter distance of 80 cm. Patient immobilization was required to assure treatment reproducibility. Reirradiation was delivered on an individualized basis according to the patient's clinical condition and the endoscopy and/or CT scan of the head and neck findings. The reirradiation volume was determined from clinical examination, the examination notes of the surgeon during endoscopy, and the extent of the tumor seen on CT. A combination of lateral opposing fields, or anterior and lateral wedged fields, or anterior and posterior semifields, or other arrangements were used for the recurrent tumor at the primary site and/or the neck nodes. The spinal cord was routinely excluded from the treatment beams. The median reirradiation dose was 39.8 Gy (range 24-58) and 63.1% (41/65) of the patients received ≥ 40 Gy. The median cumulative dose (initial radiation dose + reirradiation dose) was 102.9 Gy (range 84-120) and 70.8% (46/65) of the patients received a cumulative dose ≥ 100 Gy.

Assessment of response to reirradiation

Evaluation of tumor response was done 6 weeks following treatment completion. Patients were considered to have achieved CR if all detectable disease totally disappeared for at least 1 month. Partial response (PR) was defined as reduction of measurable disease by at least 50% for at least 1 month. Patients were considered to have stable disease (SD) if there was an average decrease in measurable tumor of less than 50% for at least 1 month. Progressive disease (PD) was defined as any increase in the size of any measurable or evaluable lesion, or the appearance of new lesion(s).

Clinical CR with reirradiation given for recurrence was observed in 9 (13.9%) patients, 18 (27.7%) patients had PR, 11 (16.9%) patients were with SD, and PD was present in 27 (41.5%) patients. The average duration of CR was 12.7 months (range 9-18), and for PR it was 9.1 months (range 3-18). The median time to disease progression in patients with objective response (CR + PR) was 10.3 months (range 3-18), while the median time to disease progression in patients with SD was 3.7 months (range 1.5-7).

Survival from recurrence

PFS, i.e. the duration of response, was measured from the beginning of reirradiation to the date of disease progression or the date of last patient's visit. Patients with PD were assigned a PFS of 0 months. PFS at 1 year was 13.4% (Figure 1). The median duration of PFS was 4.9 months (range 0-18).

OS was calculated from the date of first treatment of the recurrence to the date of death or last contact with the patient. OS at 1 year was 27.7% (Figure 1).

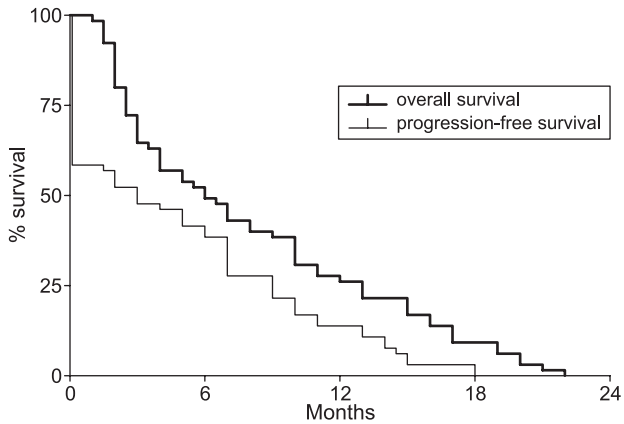

Figure 1. Kaplan-Meier curves of overall and progression-free survival after reirradiation for recurrent head and neck cancers.

The median duration of OS was 8 months (range 1-22). At the time of analysis no patient was alive.

Analyzed prognostic factors

The relative importance of a number of potential prognostic factors aimed at predicting the value of reirradiation for recurrent HNC was investigated. The analyzed prognostic factors related to patient were age and gender. The analyzed prognostic factors related to primary tumor characteristics were topography of the initial primary lesion (oral cavity vs. oropharynx vs. hypopharynx vs. larynx vs. nasopharynx vs. nasal cavity and paranasal sinuses), initial tumor size (T2 vs. T3 vs. T4), initial nodal involvement (N– vs. N+) and type of initial treatment (postoperative radiotherapy vs. definitive radiotherapy vs. concurrent chemoradiotherapy). The prognostic factors related to the characteristics of recurrence were KPS at the time of relapse (70-80 vs. 90-100%), site of recurrence (site of primary tumor vs. cervical nodes vs. both), response to reirradiation (CR vs. PR vs. SD vs. PD), dose to recurrence (< 40 vs. ≥ 40 Gy), cumulative dose (< 100 vs. ≥ 100 Gy) and DFI interval (≤ 6 vs. > 6 months).

Statistical analysis

All variables were evaluated by univariate analysis to assess their impact on OS and PFS. OS and PFS have been estimated as a function of time by Kaplan-Meyer method. The significance of the relation of certain factors with OS and PFS was tested by log-rank test [14] and p-value. Statistical significance was considered when p-value was <0.05. The Cox regression model was used to reveal the significance and independence of each prognostic factor [15].

Results

Univariate analysis

Significant factors influencing OS and PFS rates were the initial tumor site, initial tumor size (T stage), KPS, response to reirradiation, radiation dose to recurrence, cumulative radiation dose and DFI (Tables 2 and 3):

Initial tumor site. Patients with nasopharyngeal or oropharyngeal primary lesions as well as patients with tumors of the nasal cavity and paranasal sinuses had better OS compared to the group of patients with primary tumors originating from the oral cavity, larynx, or hypopharynx (p=0.0443). The initial tumor site was not found to correlate significantly with regard to PFS.

Initial tumor size (T stage). Tumor stage before the commencement of the initial treatment was significantly correlated with better OS (p=0.0288) and PFS (p=0.0299). The most favorable impact on OS and PFS was seen in T3 primary lesions.

KPS. KPS of 90-100% had highly favorable impact on OS (p<0.0001), and also on PFS (p<0.0001).

Response to reirradiation. Response to irradiation was also a statistically significant factor influencing OS (p<0.0001) (Figure 2) and PFS (p<0.0001) (Figure 3). OS and PFS rates were significantly better in patients with CR and PR compared either to patients with SD or PD.

Dose to recurrence. There were significant differences in OS (Figure 4) and PFS rates between the groups of patients receiving different radiation doses to the recurrent tumor. OS and PFS were significantly better in patients with doses ≥ 40 Gy compared to the group of patients with doses < 40 Gy (p<0.0001, both).

Cumulative dose. Cumulative dose had a significant impact on OS. Patients with cumulative dose ≥ 100 Gy had significantly better OS compared to patients with cumulative dose < 100 Gy (p<0.0001). Cumulative dose had no significant impact on PFS.

DFI. DFI was identified as a significant prognostic factor for both OS and PFS. Patient with DFI longer than 6 months had significantly better prognosis, both in terms of OS and PFS (p=0.0016 and p=0.0142, respectively).

Multivariate analysis

The results of Cox regression analysis indicated response to reirradiation (p<0.0001) and the radiation dose to the recurrence (p=0.049) as significant independent prognostic factors for OS (Table 4). The only significant independent prognostic factor correlated with PFS was response to reirradiation (p=0.0008; Table 5).

Table 2. Univariate analysis for overall survival

Factor	*Patients n*	*Median OS (months)*	*1-year survival (%)*	*p-value*
Age (years)				
< 70	58	8.4	29.2	NS
≥ 70	7	5.1	14.3	
Gender				
Male	60	7.7	25.3	NS
Female	5	11.5	39.1	
Initial tumor site				
Oral cavity	13	6.1	22.9	0.0443
Oropharynx	8	8	12.3	
Hypopharynx	7	4.1	0	
Larynx	24	7.1	20.7	
Nasopharynx	11	13.5	72.7	
Nasal cavity and paranasal sinuses	2	15.5	49.6	
Initial tumor size				
T2	13	7.6	30.6	0.0288
T3	31	10.0	42.0	
T4	21	5.4	4.6	
Nodal involvement				
N–	25	7.9	19.8	NS
N+	40	8.1	29.7	
Type of initial treatment				
Postoperative RT	32	7.6	21.3	NS
Definitive RT	22	7.2	18.3	
Concurrent chemo-RT	11	10.9	54.3	
Site of recurrence				
Primary site	17	9.1	29.3	NS
Neck only	27	8.6	29.8	
Both	21	6.5	18.8	
KPS				
70-80	36	4.8	2.7	<0.0001
90-100	29	12.1	55.5	
Response to reirradiation				
Complete response	9	17.2	88.9	<0.0001
Partial response	18	12.5	55.5	
Stable disease	11	6.5	0	
Progressive disease	27	2.6	0	
Radiation dose to recurrence (Gy)				
<40	24	2.6	0	<0.0001
≥40	41	11.2	41.3	
Cumulative radiation dose (Gy)				
<100	19	2.7	0	<0.0001
≥100	46	10.2	36.6	
DFI (months)				
≤ 6	15	4.6	6.6	0.0016
> 6	50	9.1	32.2	

NS: not significant, RT: radiotherapy, KPS: Karnofsky performance status, DFI: disease free interval, OS: overall survival

Discussion

The appearance of local or locoregional recurrence of squamous cell HNC in a substantial period of time after completion of the initial treatment represents a serious problem that radiation oncologists are not so rarely faced with. Recurrences appear in approximately two thirds of patients by 6 months and about 40-60% of patients die without evidence of disease elsewhere in the body [16]. Patients with recurrent squamous cell HNC included in our retrospective study were treated with external beam reirradiation as the only treatment modality.

Regarding the poor prognosis of this patient population, a reasonable effort was made to improve the re-

Table 3. Univariate analysis for progression-free survival

Factor	*Patients n*	*Median PFS (months)*	*1-year survival (%)*	*p-value*
Age (years)				
< 70	58	5.3	14.1	NS
≥ 70	7	2	13.4	
Gender				
Male	60	4.6	11.6	NS
Female	5	8.2	39.7	
Initial tumor site				
Oral cavity	13	3.2	0	NS
Oropharynx	8	5.1	11.5	
Hypopharynx	7	1.7	0	
Larynx	24	4.1	12.2	
Nasopharynx	11	9.6	40.9	
Nasal cavity and paranasal sinuses	2	10.5	50.3	
Initial tumor size				
T2	13	4.2	22.9	0.0299
T3	31	6.9	19.2	
T4	21	2.4	0	
Nodal involvement				
N–	25	4.6	9.8	NS
N+	40	5.1	19.8	
Type of initial treatment				
Postoperative RT	32	4.4	9.3	NS
Definitive RT	22	4.6	18.3	
Concurrent chemo-RT	11	7.0	18.3	
Site of recurrence				
Primary site	17	5.8	23.3	NS
Neck only	27	5.7	18.3	
Both	21	3.1	0	
KPS				
70-80	36	2.2	0	<0.0001
90-100	29	8.3	30.9	
Response to reirradiation				
Complete response	9	12.7	55.5	<0.0001
Partial response	18	9.1	22.2	
Stable disease	11	3.7	0	
Progressive disease	27	0	0	
Radiation dose to recurrence (Gy)				
<40	24	0.3	0	<0.0001
≥40	41	7.7	21.7	
Cumulative radiation dose (Gy)				
<100	19	0.3	0	NS
≥100	46	6.8	19.1	
DFI (months)				
≤ 6	15	2.3	0	0.0142
> 6	50	5.7	17.8	

PFS: progression-free survival. For other abbreviations see footnote of Table 2

sults of treatment mainly by using concomitant chemotherapy and reirradiation as management of recurrences of squamous cell HNC [17-21].

Since at our institution there is no standard treatment modality for these patients, we usually begin retreatment of patients with recurrent HNC in previously irradiated areas by using concurrent chemoradiotherapy. From the standpoint of the necessity of having correct and precise assessment of the impact of a new treatment modality on the clinical outcome of patients with recurrent HNC, we considered that the definition of prognostic factors that could influence the duration of patient survival to be of major importance.

The multivariate analysis in this study revealed

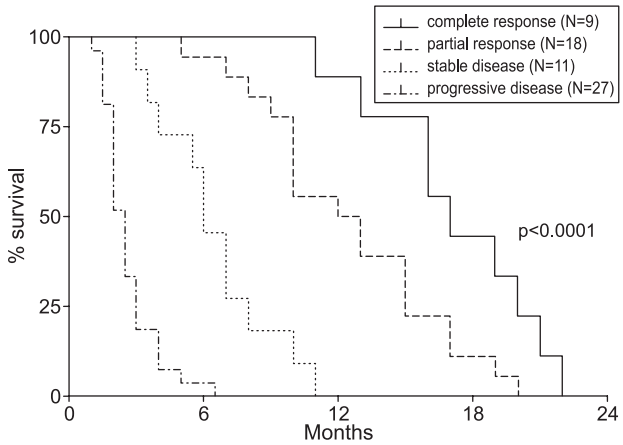

Figure 2. Kaplan-Meier curves of overall survival by response to reirradiation.

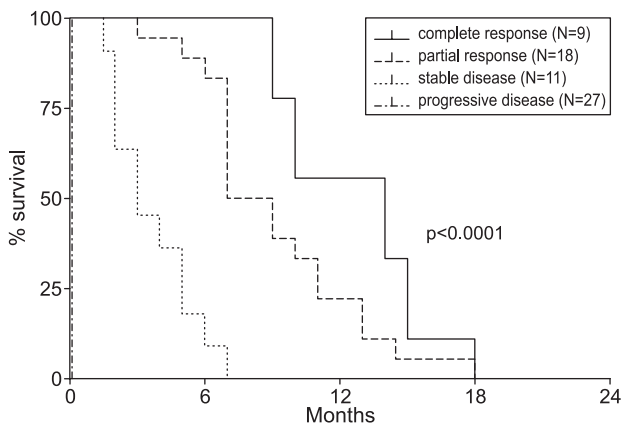

Figure 3. Kaplan-Meier curves of progression-free survival by response to reirradiation.

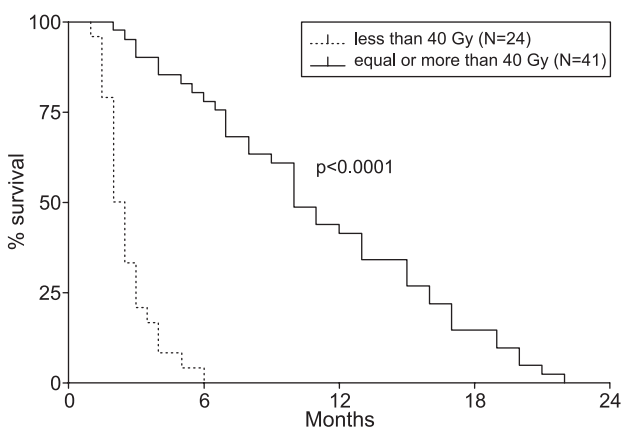

Figure 4. Kaplan-Meier curves of overall survival by dose to recurrence.

that response to reirradiation and radiation dose to the recurrent site were significant independent prognostic factors for OS, while response to reirradiation was significant independent prognostic factor for PFS.

Table 4. Multivariate analysis for overall survival

Factor	*HR*	*p-value*
Initial tumor site	0.712	0.841
Initial tumor size	1.465	0.076
KPS	0.696	0.337
Response to reirradiation	4.460	<0.0001
Radiation dose to recurrence	0.290	0.049
Cumulative radiation dose	1.041	0.935
DFI	0.860	0.662

HR: hazard ratio, KPS: Karnofsky performance status, DFI: disease free interval

Table 5. Multivariate analysis for progression-free survival

Factor	*HR*	*p-value*
Initial tumor size	1.154	0.545
KPS	1.168	0.726
Response to reirradiation	18.085	0.0008
Radiation dose to recurrence	0.595	0.389
Cumulative radiation dose	1.016	0.972
DFI	1.305`	0.479

For abbreviations see footnote of Table 4

In the prospective study of Schaefer et al. [11] testing the effectiveness of combined chemotherapy and radiotherapy for recurrent HNC, response to treatment was also identified as a prognostic factor that had great influence on OS and PFS. In the study of Argiris et al. [9] conducted to identify prognostic factors in patients with recurrent or metastatic HNC who were treated with cisplatin-based combination chemotherapy in two randomized phase III trials conducted by the Eastern Oncology Cooperative Group (ECOG), response to chemotherapy was found to be independent predictor of survival. Response to chemotherapy for recurrence was also found to be significant independent prognostic factor for OS in the study by Recondo et al. [22] who studied 90 patients treated in 4 prospective cisplatin-based phase II studies.

The repeated radiation dose was independently prognostic for OS ad PFS in the study of Salama et al. [21] suggesting that the probability for achieving objective response in this setting increases by improving the dose intensity. Several authors emphasized the necessity of delivery of a full dose of radiation in patients with nonresectable recurrent HNC as the only chance for achieving locoregional control [20,23-25]. In the study of Schaefer et al. [11] radiation dose was found to be one of the prognostic factors that influenced OS as well as PFS. Haraf et al. [26] reported that radiation dose was the most important factor associated with OS, PFS and local disease control.

In the retrospective study of Datta et al. [27], ra-

diation dose to recurrence was found as primary and important independent prognosticator for OS. In contrast, the investigation by Ohizumi et al. [28], who analyzed outcomes and prognostic factors to assess the value of reirradiation for recurrent HNC, did not find reirradiation dose being significant.

In our study no prognostic factor related to patient or to primary tumor characteristics was identified as significant for OS and PFS. The prognostic factors related to characteristics of recurrence that significantly influenced OS were response to reirradiation and radiation dose to recurrence. Current evidence indicates that response to treatment of recurrent HNC, irrespective of treatment modality used, is one of the most important prognostic factors influencing patients' outcome. Considering the fact that concurrent chemotherapy improves the effectiveness of reirradiation and can lead to increasing the objective response rates it could be concluded that concurrent chemoradiotherapy appears to be justified in patients with recurrent HNC. A higher radiation dose to the recurrence is also expected to be more effective, enabling enhancement of response rates and consequently positively impacting OS and PFS.

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