THE NEW ARMENIAN MEDICAL JOURNAL
Vol. 3 (2009), N 3, 11-21
www.ysmu.am

POSTOPERATIVE RADIOTHERAPY VERSUS CONCURRENT RADIOCHEMOTHERAPY FOR LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY AND THE OROPHARYNX. A RETROSPECTIVE ANALYSIS OF HIGH-RISK PATIENTS.

Kuhnt[1] T., Klockenbrink U. *[2b)], Pelz T.[3], Wienke A.[4], Janich M.[3], Sandner A.[5], Lautermann J.[6], Vordermark D.[3], Schubert J.[2a)]

[1] University Hospital Rostock, University of Rostock; Department of Radiation Oncology; Rostock, Germany
[2a)] Department of Oro- Maxillofacial Surgery, University Hospital Halle, Martin–Luther-University Halle-Wittenberg, Halle, Germany
[2b)] Department of Oro-Maxillofacial Surgery, University Hospital Halle, Martin–Luther-University Halle-Wittenberg, Germany
[3] Department of Radiation Oncology, University Hospital Halle, Martin–Luther-University Halle-Wittenberg, Halle, Germany
[4] Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University Halle-Wittenberg, Halle, Germany
[5] Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Halle, Martin–Luther-University Halle-Wittenberg, Halle, Germany
[6] Department of Otorhinolaryngology, Head and Neck Surgery, Hospital Martha-Maria, Halle, Germany

Abstract

The squamous cell carcinoma of the head and neck is highly malignant disease with a poor prognosis, reflecting the mature history of this disease to growth rapidly on primary site and disseminate early in the regional neck lymph nodes. Most patients have locally advanced disease at the time of diagnosis. In case of non-resectability primary radiochemotherapy (XRCT) is used as the standard treatment for those tumors.

This report summarizes the results of a postoperative radio- vs. radiochemtherapy in patients with high-risk UICC stage III and IV A,B oral cavity and oropharnyx cancer.

It is a non randomized, retrospective review of 195 cases. The Kaplan-Meier progression-free and over-all- survival rate show a slightly, non significant survival benefit in favour of the combined therapy group. A 5-year locoregional-control rate after radiotherapy and radiochemotherapy of 62% and 78%, respectively, ($p = 0.19$) was reached. The estimated 5-year cumulative incidence of distant metastases was greater in the XRCT-group, the differences were not significant. The total incidence of second primary tumor was 7%, all in patients with XRT. The results agree predominantly with the data of the three other studies. The survival advantage for the combination group over the radiotherapy alone was mainly reached by better locoregional tumor control. However, it's known that there are different survival rates for diverse tumor sites. Therefore, we included only patients with carcinoma from the oral cavity and oropharynx. Both tumor sites reached survival advantage by an increase of locoregional control rate. Unambiguously, there is no significance in the rates of progression- free, overall and locoregional survival because of the higher rate of distant metastases in the XRCT-group. This could be explained by the fact that the dose and the acting mechanism of the drugs applied during irradiation only was sufficient to enhance the effect of irradiation, but did not have a systematic effect.

Address for Correspondence:
Ulf Klockenbrink; Department of Oro- Maxillofacial Surgery,
University Hospital Halle (Saale); Ernst-Grube-Str. 40;
Halle (Saale) D-06120 Germany;
Tel.: +49.345.557.3314; Fax: +49.345.557.7070;
Email: ulfklockenbrink@yahoo.de

Some side-effects were greater observed in the combined therapy-group than in the radiotherapy group which is in concordance with the results of all studies of this topics.

Thus the results of superiority of XRCT vs. XRT have to be evaluated against the background of greater higher side-effects and a more intensive supportive care.

Above all patients with a R1 resection should be treated with a XRCT. More and more the certainty becomes that the concomitant platinum-based chemotherapy has no impact on ECS and distant metastases. In case of N2b-3 situation the patients should be supplied with newer therapy strategies. Most probably, intensifying or prolongation of systematic treatments incorporating polychemotherapy and biologic agents might reduce distant failures. Furthermore, prospective phase-III-studies are needed to compare the effect of organ-preserving/sparing therapies with traditional combined surgery and XRT/XRCT determine the effect on functional outcome and quality of life. These concepts should combine the effectiveness of a systemic treatment with the safety of a limited surgical resection of the tumor site to preserve as much function as possible

Keywords: head and neck carcinoma, high- risk- patients, radiochemotherapy, cisplatin, survival, side effects.

Introduction

The squamous cell carcinoma (SCC) of the head and neck is highly malignant disease with a poor prognosis, reflecting the mature history of this disease to growth rapidly on primary site and disseminate early in the regional neck lymph nodes. Most patients have locally advanced disease at the time of diagnosis [*Forastiere A. et al., 2001*]. In case of non-resectability the primary radiochemotherapy (XRCT) is used as the standard treatment for those tumors [*Budach W. et al*., *2006*].

In 1994, the European Organization for Research and Treatment of Cancer (EORTC) the EORTC trial 22931, the Radiation Therapy Oncology Group (RTOG) the RTOG trial 95-01 and in 1998, the Arbeitsgemeinschaft Radioonkologie der Deutschen Krebsgesellschaft (ARO) the ARO trial 98-01, randomized trials were initiated [*Bernier J. et al., 2004; Cooper J. et al., 2004; Fietkau R. et al., 2006*]. Before publication of the results of these studies its therapy advantage was unclear, and the indication was at the discretion of the treating physician. Due to the expected greater acute and chronic side effects, older ages of patients or the worse patient's general conditions, doctors declined a postoperative XRCT. Moreover, the placing of an elective, percutane endoscopic gastrostomy tube was refused by some patients. However, two of the three recent randomized multicentre trials showed a clear survival benefit to adjuvant XRCT compared to XRT alone. It is thought to be the treatment of choice for operable locally advanced high-risk stage III/IV A,B tumors with 5-year survival rates from 45-58% [*Bernier J. et al., 2004; Cooper J. et al., 2004; Fietkau R. et al., 2006*]. However, also after surgery plus XRCT treatment, 11-26% of those patients develop second primary malignancy and 20-35% experience distant metastases over a period of 5 years [*Di Martino E. et al., 2002; Vaamonde P. et al., 2003*].

We retrospectively reviewed the records of all patients presenting to the Martin-Luther-University Halle-Wittenberg with previously untreated SCC from 1997 to 2006. A limitation of present studies of the head and neck region is that it summarizes various tumor sites of SCC. However, it is, known that there are very different survival rates of diverse tumor sites [*Gourin C. and Johnson J., 2001; Carvalho A. et al., 2005*]. Therefore, we have confined only patients with carcinoma of the oral cavity and oropharynx in our review. Hence, we hope to evaluate a more homogeneous patient cohort.

In the present study the results of an application of low-dose cisplatin concurrent to radiotherapy were analyzed. The greatest differences between the cisplatin based adjuvance XRCT trails regarding this issue consisted in the choice of single and total dose of cisplatin. In both RTOG and EORTC study cisplatin was administered three times with 100 mg/m^2 on day 1, 22, 43 [*Bernier J. et al., 2004;* ,*Cooper J. et al., 2004*].

On the other hand, in the German ARO study cisplatin was fractionated over 10 days of 20 *mg/m²/d* administered on days 1-5 + 29-33 [*Fietkau R. et al., 2006*]. So far, the specific efficacy of the above mentioned concomitantly used cisplatin dosages was not compared in randomized prospective trials. Recently, D. Rades and co-authors compared in a non-randomized study the two radiochemotherapy regimens for toxicity in patients with stage III/IV head and neck cancer [*Rades D. et al., 2008*]. The authors concluded that two courses of fractionated cisplatin (20 *mg/m²/d*) and 5-FU were associated with significantly less acute toxicity and with better compliance than three courses of cisplatin (100 *mg/m²/d*).

Aim:

The objective of this retrospective, single-centre study was to determine whether the addition of chemotherapy (with cisplatin alone or cisplatin + 5-FU) to high-dose radiotherapy after radical surgery increases progression-free survival (PFS), overall survival (OS) and regional control rate (LCR) in patients at high-risk cancer of oral cavity or oropharynx. Secondary endpoints of reviewing included acute and late adverse effects.

Methods

Patient Population and Eligibility Criteria. The stage of the tumor was determined on the basis of the histologic findings and classified according to the criteria of the Union Internationale contre le Cancer [*Spiessl B. et al., 1989*]. All patients underwent a full endoscopic examination during which a diagram was made of the extent of disease. Computed tomography (CT) and/or MRT of the site of the primary tumor and the neck were obligate. CT of chest, serum chemical analyses, and a complete blood count were obtained.

To be eligible, patients had to have a histologically proven SCC arising from the oral cavity or oropharynx with a tumor (T) stage of pT1-3 (alone + the risk factor R1) or pT4 and any nodal stage (N), a tumor stage of I or II with a nodal stage of pN2b (> 2 metastatic involved lymph nodes) or pN3 and no distant metastasis (M0). Patients who had unfavourable pathological findings such as extracapsular nodal spread, positive resection margins (R1) or perineural involvement were also eligible, as were those with oral cavity or oropharynx tumors with involved lymph nodes at level IV or V, according to the proposed anatomical lymph-node distribution [*Robbins K. et al. , 1991*].

Patients had to be at least 18 years of age and no older than 75 years, with a Karnofsky performance status of > 60%, they also had to have a serum creatinine concentration below 120 *µmol per liter*, a white-cell count at least 4.0 *GpT/liter,* a platelet count of at least 100 *per GpT/millimeter*, and hemoglobin concentration of at least 6.8 *mmol per liter* (11.0 *g per deciliter*). Aminotransferase values and bilirubin values could not exceed twice the upper limit of normal. Patients who had a history of invasive or synchronous cancer, except non-melanoma skin cancer, had previously received chemotherapy, or had known central nervous system disease were excluded from the study.

Surgery. All patients underwent an initial surgery performed with the intention of curing. The extent of the surgical resection depended on the volume and the tumor site of the primary tumor. Neck-dissection procedures followed accepted criteria for adequate excision. If there was a tumor distance of less than 5 *mm* related to a surgical margin, the resection was considered to be close and defined as close margin (R1).

Radiotherapy. Treatments were conducted on linear accelerators of 6 *MV* with the use of isocentric techniques. All patients were immobilized in thermoplastic head-neck-and-shoulder masks with treatment-planning CT scans for defining target volumes. The CT scans (slice thickness 5 *mm*) the clinical target volumes (CTV), the spinal cord and both parotids were delineated. For the 2D-technique (2D-T1) a parallel opposed field photon/electron irradiation was used and for technique 2 (3D-T2) a combination of a static coplanar and dynamic portal irradiation with 11 portals was designed. All patients received postoperative radiotherapy consisting of conventionally fractionated doses of 2 *Gy* each in five weekly sessions. Maximal and minimal target-volume doses and the maximal dose to the spinal cord were recorded. The target volumes and doses were determined from clinical information, operative findings, or CT/MRI. Two clinical target volumes (CTV) were defined: CTV_{70} (70 *Gy* dose) for high-risk target volumes (*i.e.*, R1 without chemotherapy), CTV_{64} (64 *Gy* dose) for high-risk target volumes (*i.e.*, R1, EC, or nodal regions with ≥3 nodes involved with concurrent chemotherapy), and CTV_{50} (50 *Gy* dose) for low-risk regions (*i.e.*, prophylactic nodes

down to the clavicles in both groups). Planning target volume was defined as the CTV plus a 5- to 10-*mm* margin to compensate for variables of treatment setup and internal organ motion. The treatment fields varied with tumor site. Oral tongue and floor of mouth primaries had a posterior border lying anterior to the spinal cord. The dose to the spinal cord was limited to 45 *Gy*.

Chemotherapy. Chemotherapy consisted of 20 *mg* of cisplatin per square meter of body-surface area on days 1 to 5 and 29 to 33 plus 5-FU 600 *mg* per square meter of body-surface area on days 1 to 5 and 29 to 33 as 120 hours continuous infusion (group A) or 25 *mg* cisplatin per square meter of body-surface area on days 1 to 5 and 29 to 33 (group B) of the entire course of radiotherapy. On each day of cisplatin administration, the patients received 8 *mg* of ondansetrone and 8 *mg* dexametasone and 500 *mL* of hydration plus mannitol 250 *mL* given over 60 minutes before administration of cisplatin. Cisplatin was administered over 30 minutes solved in 500 *mL* 0.9% natrium chloride. The irradiation was given immediately afterwards during 30 minutes. After that, we administered another 250 *mL* mannitol and 1000 *mL* of hydration. Furthermore, the hydration and antiemetics were continued the following three days until all chemotherapy associated symptoms were abated. The chemotherapy was administered only by the radiation oncologists.

In radiation period acute toxicities were graded according to NCI common toxicity criteria (CTC) Version 2.0 once weekly. Late toxicities were registered in accordance with the RTOG/EORTC-system. For toxicity analysis the most severe adverse effects of each patient were rated.

Follow-up. Patients were evaluated every 3 months for the first 6 months, every 6 months for the next 24 months, every 12 months for the next 3 years, and annually thereafter. Adverse effects, weight, performance status, and tumor response were assessed at baseline, weekly for the first eight weeks, and at each follow-up assessment. CT/MRT were required 6 weeks after the end of adjuvant therapy and then once per year over a period of 5 years.

Statistics. We compared these patients groups on the basis of histopathologic findings, surgical protocols, radiotherapy documents, and follow-up reports. The primary endpoints were locoregional control rate (LC), progression-free survival (PFS), overall survival (OS) and patterns of failure (POF). Toxicities were secondary endpoints. Locoregional control was defined as the time from diagnosis to the occurrence of a local or regional recurrence. Progression-free survival was defined as the time from diagnosis to the time of an appearance of a locoregional recurrence or systematic metastasis. Overall survival was defined as the time from diagnosis to death from any cause.

SPSS 15.0 statistical software was used for all analyses (SPSS Inc., Chicago, IL). The Kaplan-Meier method was used for calculation of LC, PFS, and OS [*Kaplan E. and Meier P., 1958*]. Toxicity rates were compared using the chi-square test or Fisher's exact test. For comparison of the statistical significance of the survival curves the log-rank test was used. Multivariate analyses with the Cox proportional hazards model were used to test the independent significance by backward elimination of insignificant variables of different parameters. In univariante analyses and a p value of < 0.5 and in multivariant analyses a p value of < 0.1 was adopted to suggest statistical significance.

Results:

Characteristics of Patients. From 1997 to 2006, records from 195 patients were reviewed. The pretreatment patient characteristics are illustrated in Table 1. In the examination 81% were men and 76% were above 50 years of age. Of these 195 patients, 134 (69%) receive radiotherapy alone and 61 (31%) receive concurrent chemotherapy and radiotherapy. In 189 (97%) of cases a radical or a radical modified and in 6 (3%) a selective suprahyoidal neck dissection was performed. The baseline characteristics of the two groups were not equal in all parameters. The group of combined treated patients exhibited more tumors of oropharynx and worse level of disease, i.e. in R1 and T-stage. The median follow up times were 40 months for both groups and the maximal follow-up time 120 months in the radiotherapy group and 108 months in the combined-therapy group, respectively.

Treatmen. The median and standard deviation (sd) of the total dose of radiation were the radiation group 65Gy (sd 2.7) and in the combined group 66 *Gy* (sd 2.8). The median duration of treatment from time of surgery to the end of irradiation was 84 days (sd 13 days), ranging 60 to 138 days in

Table 1.

Characteristics of patients and tumors

Characteristic/ Number (%)	XRT* n= 134(%)	XRCT** n= 61(%)	Total n= 195(%)	Significance p
Gender				
Male	105(78)	53(87)	158(81)	0.16
Female	29(22)	8(13)	37(19)	
Age				
Median- years	58(sd 9.7)	53(sd 7.9)	56(sd 9.4)	0.32
Range-years	25-79	33-76	25-79	
Karnofsky performance status (KPS)				
KI 60 (%)	0(0)	1(2)	1(1)	
KI 70 (%)	23(17)	11(18)	34(16)	
KI 80 (%)	42(31)	12(20)	54(28)	0.26
KI 90 (%)	59(44)	30(49)	89(46)	
KI 100 (%)	10(8)	7(11)	17(9)	
Primary Tumor Site				
Cavity of mouth	67(50)	22(36)	89(46)	0.07
Oropharynx	67(50)	39(64)	106(54)	
pT Stage*				
pT1	11(8)	7(12)	18(9)	
pT2	45(34)	19(31)	64(33)	0.25
pT3	37(28)	10(16)	47(24)	
pT4	41(30)	25(41)	66(34)	
pN Stage*				
pN0	32(23)	19(31)	51(26)	
pN1	21(16)	6(10)	27(14)	
pN2a	10(8)	0(0)	10 (5)	0.045
pN2b	61(45)	26(43)	87(45)	
pN2c	10(8)	10(16)	20(10)	
UICC Stage				
I	1(1)	0(0)	1(1)	
II	10(8)	4(7)	14(7)	
III	26(19)	7(11)	33(17)	0.63
IVA	26(19)	14(23)	40(20)	
IVB	71(53)	36(59)	107(55)	
Histologic Differentiation				
G1	5(4)	2(4)	7(4)	
G2	61(45)	29(47)	90(46)	0.81
G3	66(49)	30(49)	96(49)	
G4	2(2)	0(0)	2(1)	
Resection-Margin Status				
Negative (R0)	83(62)	23(38)	106(54)	**0.002**
Positive (R1)	51(38)	38(62)	89(46)	
Extracapsular Nodal Spread				
No	97(72)	37(61)	134(69)	0.10
Yes	37(28)	24(39)	61(31)	

The tumor (T) and nodal (n) were determined on the system of the Union Internationale contre le Cancer (UICC). Abbreviations: *XRT = radiotherapy; **XRCT = radiochemotherapy.

Table 2.

Toxicity graduation

Toxicity	XRT*		XRCT**		p
	Grade 3 (%)	Grade 4 (%	Grade 3 (%)	Grade 4 (%	
Hematologic					
Leukopenia	33 (22%)	1 (1%)	23 (38%)	2 (3%)	**0.03**
Anaemia	18 (13%)	0	9 (15%)	0	0.97
Renal failure	0	0	1 (1%)	0	0.93
Hematologic					
Leukopenia	0	0	15 (25%)	0	**0.001**
Anaemia	(1%)	0	1 (1%)	0	0.90
Renal failure	0	0	0	1 (1%)	0.90

*XRT = radiotherapy; **XRCT = radiochemotherapy

the radiotherapy group and 81 days (sd 13 days), in the range of 55 to 130 days in the combined-therapy group. Cisplatin + 5-FU was given in 39/61 (64%) cases and cisplatin alone in 22/61 (36%) cases. In 5 patients (8%) the 2nd cycle was not administered.

Severe Acute Adverse Effects. Acute severe grade 3 or higher mucositis and leucopenia were significantly greater in the combined-therapy group than in the radiation group, incidence 41% vs. 25%; p = 0.03, 25% vs. 0%; p = 0.001. Severe (grade 3/4) nausea or vomiting were observed in the combined-therapy group vs. radiotherapy group 11% vs. 1%; p = 0.02 (Table 2). The intensive prophylactic application of antiemetics prevented these. The incidence of renal function impairment was low. In the combined therapy group vs. radiotherapy group grad 1 in 8/61 (13%) vs. 2/134 (1%), grad 2 in 1/61 (2%) vs. 1/134 (1%) and 1/61(2%) grade 4 in the combined group was observed. In 37/61 (61%) and 18/61 (29%) of patients of the radio-chemotherapy group and in 38/134 (28%) and 10/134 (7%) of the patients of the radiotherapy group oral antibiotics (Ciprobay® and Clont®) and blood transfusions, respectively, were given; p = 0.001, p = 0.001. The use of EPO occurred only in 3 patients (Table 3). The incidence of serve erythema and xerostomia was equal in both groups, in the combined-therapy group vs. radio-therapy group 15% and 11% vs. 13% and 12%; p = 0.09, p = 0.03.

Progression-Free Survival. After a median follow-up of 40 months (sd 23.6 months, range: 1 to 120 months), a total of 84 (43%) treatment failures (local and distant) had been recorded. The estimated median duration of progression-free survival in the radiotherapy group was 72 months (CI 95%, 40 to 104 months) and 78 (CI 95%, - to – months) in the combined therapy group, and the Kaplan-Meier estimates of 5-year progression-free survival were 52 % and 54 %, respectively. There was no advantage difference of the combined group over the radiotherapy group, p = 0.8 by the Log-rang test (Figure 1). The disease progressed in 59/134 (44%) in the radiotherapy group and in 25/61 (41%) in the combined therapy group.

Overall survival. The 5-year overall survival rate of all patients was 51% (sd 4%). A total of 88

Table 3.

Supportive care

Toxicity	XRT* n = 134	XRCT** n = 61	p
	yes	yes	
Blood transfusion	10 (7%)	18 (29%)	**0.001**
Antibiotics	38 (28%)	37 (61%)	**0.001**

*XRT = radiotherapy; **XRCT = radiochemotherapy

(45%) patients died. The Kaplan–Meier estimates of overall survival at 5-years were 49% in the radiotherapy group and 54% in the combined-therapy group, p = 0.8 by the Log-rank test (Figure 2). The 5-year overall survival rate was 41% for oral cavity and 62% for oropharynx tumors. The estimated median time to death was in the radiotherapy group for both tumor sites 63 months (95% CI, 49 to 77 months) with a median time of oral cavity tumors 46 months (95% CI, 26 to 66 months) and for oropharynx tumors 86 months (95% CI, 58 to 114 months) and in the combined-therapy group for both 85 months (95% CI, 42 to 128 months) and for oral cavity tumors a median time was not reached and for oropharynx tumors 85 months (95% CI, 44 to 126 months). Oral cavity or oropharynx cancer was the cause of death in 67/195 (34%) patients, 48/134 (36%) in the radiotherapy group and 19/61 (31%) in the combined therapy group. Treatment-related adverse effects were the cause of death in one patient (1%) in the radiochemotherapy group.

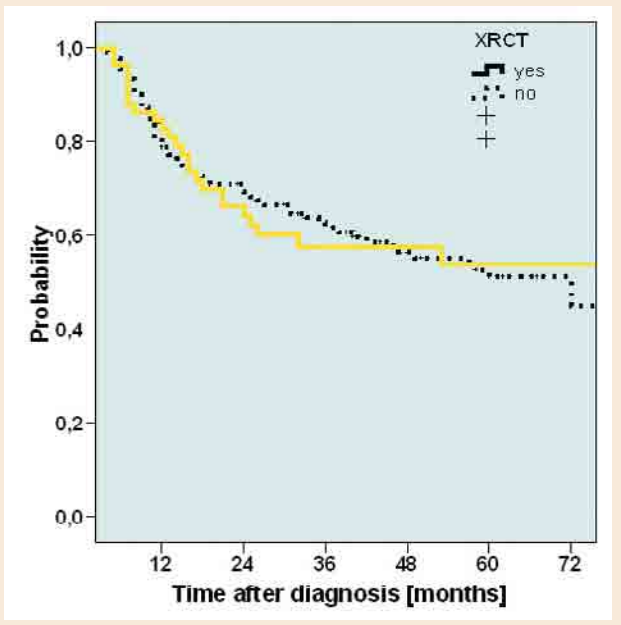

Figure 1. *Kaplan-Meier estimates of progression-free survival (PFS). Patients assigned to radiochemotherapy (XRCT) had no higher rates of progression-free survival than those assigned to radiotherapy (XRT), (p = 0.8).*

Incidence of Local and Regional Relapses.

There were 55/195 (28%) local or regional failures, 43/134 (32%) in the radiotherapy group and 12/61 (20%) in the combined-therapy group which differ with p = 0.07 (Fisher's exact test p = 0.05). The estimated five-year cumulative incidence of local and regional relapses was 46% in the radiotherapy group and 26% in the combined-therapy group (Figure 3). The difference was significant: p = 0.02.

Incidence of distant Metastases and Second Primary Tumors

The 5-year incidence of distant metastasis was 37/195 (19%), 22/134 (16%) in the radiotherapy group and 15/61 (24%) in the combined-therapy group; p = 0.17 (Table 4). In 78% the lung and in

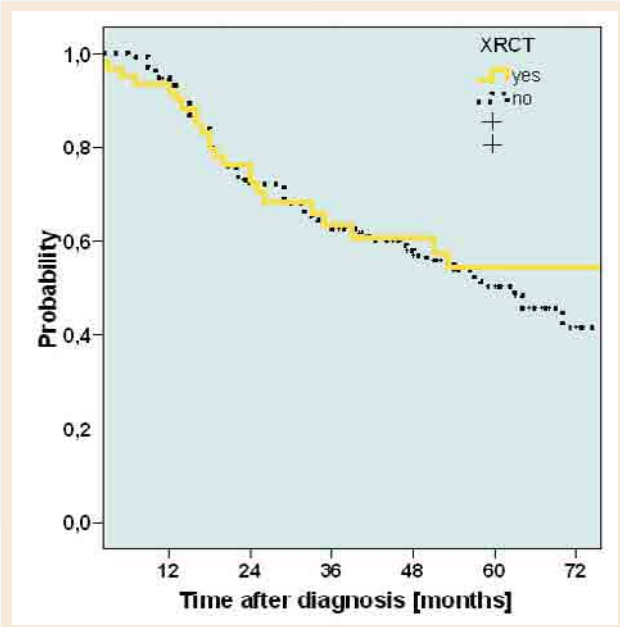

Figure 2. *Kaplan–Meier estimates of overall survival. Patients assigned to radiochemotherapy (XRCT) had no higher survival rates than those assigned to radiotherapy (XRT), (p = 0.8).*

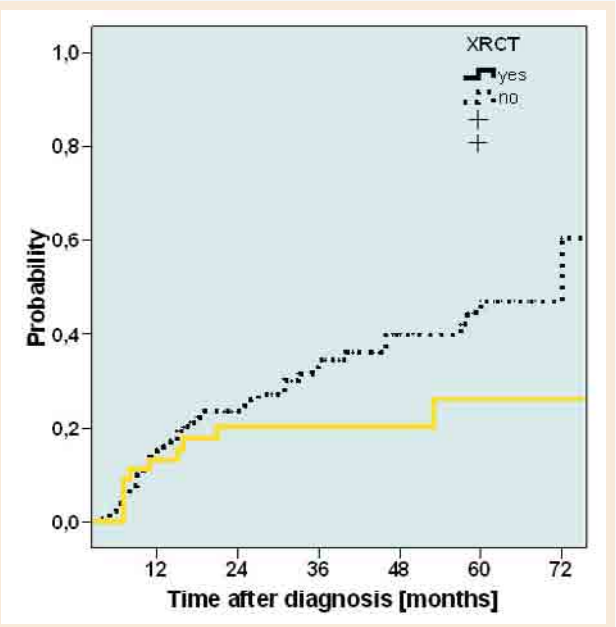

Figure 3. *Cumulative incidence of local or regional relapses. Patients assigned to radiochemotherapy (XRCT) had lower rates of local recurrences than those assigned to radiotherapy (XRT), (p = 0.02).*

Table 4.

Incidence and site of recurrence

Site	XRT* (n = 134)		XRCT** (n = 61)	
	No.	%	No.	%
Local only	26	19	7	11
Local and nodal	8	6	0	0
Nodal only	3	2	2	3
Local and nodal and distant	6	4	3	5
Total locoregional failure	4	31	12	19
Distant only	16	12	12	20
Total distant failure	22	16	15	25
Total	59	44	24	39

*XRT = radiotherapy; **XRCT = radiochemotherapy

24% the liver and bones was the place of the distant metastasis. In 9/195 (5%) patient's distant metastasis appeared synchronically to locoregional recurrence. A second primary tumor appeared in 9 cases with 0/61 (0%) patient with radio-chemotherapy and 9/134 (7%) with radiotherapy; p = 0.04. The median duration from primary diagnosis to distant metastasis and second tumor was 19.6 + 12.9 months and 41.3 + 19.6 months.

Prognostic factors. The results of multivariate analysis are shown in Table 5. The following factors were evaluated on multivariate analysis for predictive value of PFS in all patients: gender, age (<50 vs. ≥50 years), clinical T stage (T1-T2 vs. T3-T4), lymph node involvement (N0-N1 vs. N2-N3), involved lymph nodes (<2 vs. >2), resection margin status (R0 vs. R1), ECS (yes vs. no), KPS (>80 vs. <80) and concurrent chemotherapy (yes vs. no). Only the resection margin status and the Karnofsky performance status were significant factors in multivariate analysis for an increased progression - free survival. Sex, pN stage, number of involved lymph nodes and KPS were predictive factors for overall-survival. Decisive parameter for locoregional control were pN stage, resection-margin status, number of involved lymph nodes, and the use of concurrent chemotherapy.

Conclusion

This report summarizes the results of a postoperative radio- vs. radiochemotherapy in patients with high-risk UICC stage III and IV A,B oral cavity and oropharnyx cancer.

It is a non randomized, retrospective review of 195 cases. The Kaplan-Meier progression-free and over-all- survival rate show a slightly, non significant survival benefit in favour of the combined therapy group. A 5-year locoregional-control rate after radiotherapy and radiochemtherapy of 62% and 78%, respectively, (p = 0.19) was reached. The estimated 5-year cumulative incidence of distant metastases was greater in the XRCT-group, the differences were not significant. The total incidence of second primary tumor was 7%, all in patients with XRT. The results agree predominantly with the data of the three other studies [*Bernier J., et al., 2004;* ,*Cooper J. et al., 2004; Fietkau R. et al., 2006*]. The survival advantage for the combination group over the radiotherapy alone was mainly reached by better locoregional tumor control (Figure 4). However, it's known

Table 5.

Multivariate analyses of prognostic factors

End Point	Variables	ß	Exp(ß)	95% CI for Exp(ß)[6]	p
Overall survival	Sex	- 0.713	0.490	0.260- 0.923	0.027
	pN stage[1]	2.132	8.434	1.891-37.617	0.005
	>2ILN[2]	- 1.852	0.157	0.036-0.690	0.014
	KPS[3]	0.498	1.646	1.079-2.511	0.021
Progression-free survival	RMS[4]	0.584	1.793	1.163–2.765	0.008
	KPS	0.608	1.837	1.191– 2.833	0.006
Locoregional control	pN stage	2.141	8.508	1.906–37.988	0.005
	RMS	0.561	1.753	1.005 – 3.059	0.048
	>2ILN	- 2.052	0.128	0.029 – 0.569	0.007
	XRCT[5]	0.640	1.897	0.959– 3.754	0.066

[1]pN stage = pathohistological nodal stage; [2]>2ILN = > 2 of involved lymph nodes; [3]KPS = Karnofsky performance status; [4]RMS = Resection-margin status; [5]XRCT = Radiochemotherapy; [6] 95% CI, 95% = confidence interval

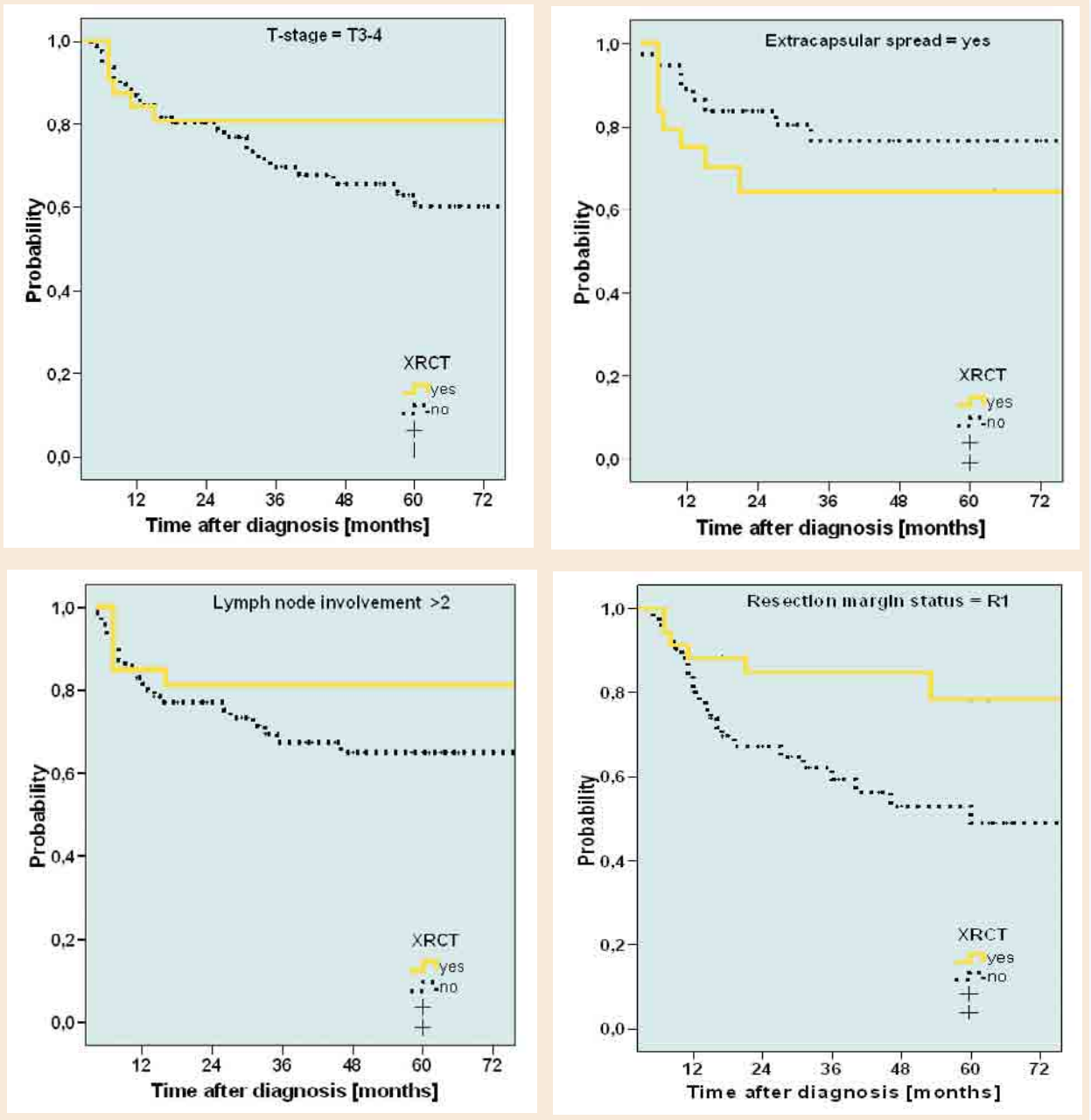

Figure 4. *Kaplan–Meier estimates and log-rank test for locoregional control. Comparison of radiotherapy (XRT) and radiochemotherapy (XRCT) regarding pT3 or 4 stage (p = 0.31), extracapsular nodal spread (p = 0.28), >2 of involved lymph nodes (p = 0.25) and positive resection-margin status (R1) (p = 0.02).*

that there are different survival rates for diverse tumor sites [*Carvalho A.L. et al., 2005; Gourin C. and Johnson J., 2001*]. Therefore, we included only patients with carcinoma from the oral cavity and oropharynx. Both tumor sites reached survival advantage by an increase of locoregional control rate (Figure 5). Unambiguously, there is no significance in the rates of progression-free, overall and locoregional survival because of the higher rate of distant metastases in the XRCT-group. This could be explained by the fact that the dose and the acting mechanism of the drugs applied during irradiation only was sufficient to enhance the effect of irradiation, but did not have a systematic effect.

Some side effects were observed to be greater in the combined therapy-group than in the radiotherapy group which is in concordance with the results of all studies of these topics [*Bernier J., et al., 2004; ,Cooper J. et al., 2004; Fietkau R. et al., 2006*].

Thus, the results of superiority of XRCT vs. XRT have to be evaluated against the background of greater higher side-effects and a more intensive supportive care.

Above all patients with a R1 resection should

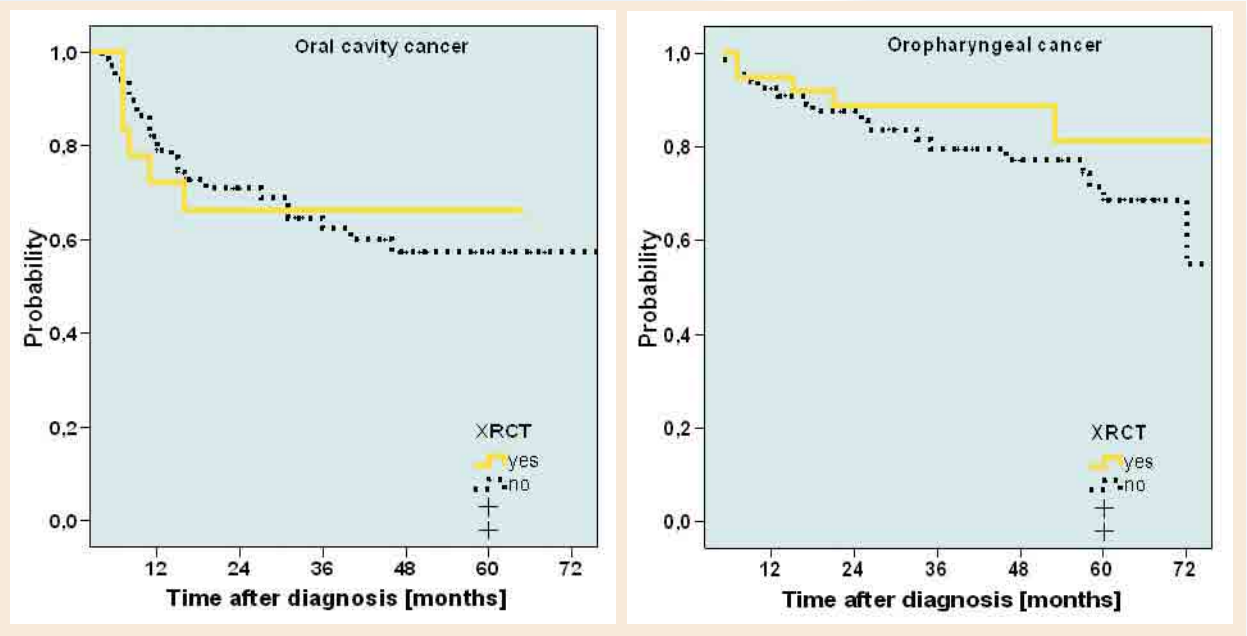

Figure 5. *Kaplan–Meier estimates of locoregional control for oral cavity cancer (log-rank test p = 0.85) and for oropharyngeal cancer (log-rank test p = 0.44).*

be treated with a XRCT. More and more the certainty becomes that the concomitant platinum-based chemotherapy has no impact on ECS and distant metastases. In case of N2b-3 situation the patients should be supplied with newer therapy strategies. Most probably, intensifying or prolongation of systematic treatments incorporating polychemotherapy and biologic agents might reduce distant failures. Furthermore, prospective phase-III-studies are needed to compare the effect of organ-preserving/sparing therapies with the traditional combined surgery and XRT/XRCT determine the effect on functional outcome and quality of life. These concepts should combine the effectiveness of a systemic treatment with the safety of a limited surgical resection of the tumor site to preserve as much function as possible.

References

1. *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.
2. *Budach W., Hehr T., Budach V. et al.* A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer. 2006; 6:.28.
3. *Carvalho A.L., Nishimoto I.N. ,Califano J.A. et al.* Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. Int. J. Cancer. 2005; 114: 806–816.
4. *Cooper J.S., Pajak T.F., Forastiere A.A. 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.
5. *Di Martino E., Sellhaus B. ,Hausmann R., et al.* Survival in second primary malignancies of patients with head and neck cancer. J. Laryngol. Otol. 2002; 116:. 831–838.
6. *Fietkau R., Lautenschläger C., Sauer R. et al.* Postoperative concurrent radiochemotherapy versus radiotherapy in high-risk SCCA of the head and neck: Results of the German phase III trial ARO 96–3. J. Clin. Oncol. 2006; 24: 5507.

7. *Forastiere A.A., Koch W., A. Trotti A. et al*. Head and neck cancer. N. Engl. J. Med. 2001; 345: 1890–1900.

8. *Gourin C.G. and Johnson J.T.* Surgical treatment of squamous cell carcinoma of the base of tongue. Head Neck 2001; 23: 653-660.

9. *Kaplan E.L. and Meier P*. Nonparametric estimation from incomplete observations. J. Am. Stat. Assoc. 1958; 53: 457-481.

10. *Rades D., Fehlauer F., Sheikh-Sarraf M. et al.* Toxicity of two cisplatin-based radiochemotherapy regimens for the treatment of patients with stage III/IV head and neck cancer. Head Neck. 2008; 30: 235-241.

11. *Robbins K.T., Medina J.E., Wolfe G.T. et al*. Standardizing neck dissection terminology: official report of the Academy's Committee for Head and Neck Surgery and Oncology. Arch. Otolaryngol. Head Neck Surg. 1991; 117: 601-605.

12. *Spiessl B., Beahrs O.H., Hermanek P. et al.* TNM atlas: illustrated guide to the TNM/pTNM-classification of malignant tumours. 3rd ed. Berlin: Springer-Verlag. 1989.

13. *Vaamonde P., Martin C. , del Rio M. et al*. Second primary malignancies in patients with cancer of the head and neck. Otolaryngol. Head Neck Surg. 2003; 129: 65–70.