

RESPONSE TO INTRAARTERIAL INDUCTION CHEMOTHERAPY: A PROGNOSTIC PARAMETER IN ORAL AND OROPHARYNGEAL CANCER

Adorján F. Kovács, MD, DMD, PhD

Department of Maxillofacial Plastic Surgery, Johann Wolfgang Goethe-University Medical School, Klinik für Kiefer und Plastische Gesichtschirurgie, Universitätsklinikum Haus 21, Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany. E-mail: A.Kovacs@em.uni-frankfurt.de

Accepted 26 October 2005

Published online 23 May 2006 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20388

Abstract: *Background.* Patients with head and neck cancer and good pathologic response to neoadjuvant systemic induction chemotherapy have a better prognosis for survival than do those with stable or progressive disease. Thus, induction chemotherapy could theoretically help in stratifying further treatment, but toxicity is much too high. The prognostic implication of superselective intraarterial high-dose cisplatin administered by a femoral approach, which has much less toxicity, is not yet known.

Methods. One hundred eighty-seven unselected consecutive patients with previously untreated oral and oropharyngeal squamous cell carcinoma received intraarterial high-dose cisplatin for induction and were assessed for response by visual examination and palpation. This treatment was followed by surgery and adjuvant radiation with concomitant systemic chemotherapy. Omission of a modality depended on individual contraindications and not on preselection. The consequence of omissions has been the constitution of several treatment arms. The overall and disease-free survival in relation to clinical local response after intraarterial induction chemotherapy was calculated using the Kaplan–Meier method. Additional analysis excluded bias caused by stages and treatment arms.

Results. Explorative statistics using the log-rank and chi-square tests demonstrated a strong prognostic relevance of response to intraarterial chemotherapy irrespective of stage and treatment.

Conclusions. Our results are encouraging for prospective randomized studies and molecular genetic investigations with intraarterial chemotherapy. © 2006 Wiley Periodicals, Inc. *Head Neck* 28: 678–688, 2006

Keywords: intraarterial chemotherapy; cisplatin; head and neck cancer; oral cancer; prognosis

It has long been known that patients with oral cancer and good pathologic response to neoadjuvant systemic induction chemotherapy have a better prognosis for survival than do those with stable or even progressive disease.¹ Therefore, induction chemotherapy theoretically would be a good prognostic parameter and could be used as a diagnostic tool to stratify further treatment. However, severe toxicities occurred quite frequently and prevented use of this modality as prognostic parameter.

In the past several years, some centers^{2–5} began using intraarterial (IA) chemotherapy in a neoadjuvant setting (before definitive treatment by surgery or radiation). A transfemoral approach and superselective perfusion have been adopted because negative catheter-related side effects can be minimized with this technique compared with retrograde approaches. The largest population

Correspondence to: A. F. Kovács

© 2006 Wiley Periodicals, Inc.

(213 patients) with neoadjuvant transfemoral IA chemotherapy was reported by Kovács et al⁶ and Kovács⁷; other investigators have reported on between 13 and 23 patients. Performing a modification of the method adopted by Robbins et al^{8,9} for the head and neck (IA high-dose cisplatin plus systemic antagonization with sodium thiosulfate), Kovács and coworkers could clinically and pharmacologically demonstrate a very low rate of acute toxicity in the neoadjuvant setting.^{6,7,10-13} From 1996 to February 2005, more than 410 patients with primary and recurrent malignancies of the head and neck were treated with IA high-dose cisplatin at our institution.

In 187 consecutive patients having sufficient observation time, response to this well-tolerated therapeutic modality was evaluated to determine possible routine application of the treatment as prognostic parameter. Our emphasis was on response reflecting tumor biology. It should be possible to detect certain tumor characteristics at an early stage of treatment. The effect of IA chemotherapy on survival itself could not be determined. Treatment modalities and toxicities will nevertheless be discussed.

PATIENTS AND METHODS

One hundred eighty-seven consecutive study patients with histologically confirmed, previously untreated primary squamous cell carcinoma (SCC) of the oral cavity and the anterior oropharynx were treated with a complex multimodality treatment regimen between December 1996 and June 2001.

This prospective pilot study was conducted to implement an integrated treatment on an unselected representative population of patients. Therefore, all consecutive patients with histologically confirmed, previously untreated primary SCC of the mentioned sites were treated with a maximum of four treatment modalities: IA induction chemotherapy, surgery, adjuvant radiation with concomitant systemic chemotherapy using docetaxel. The rationale was that no assured prognostic parameters that can direct treatment decisions exist for this cancer entity. There were no exclusion criteria. Treatment was started with IA chemotherapy, the modality with the presumed highest patient and treatment compliance. Omission of a respective modality depended on individual contraindications and refusals, not on preselection. The consequence of omissions has been the constitution of several treatment arms.

Table 1. Distribution of T and N classifications of all study patients at baseline.

T classification	No. of patients by neck lymph node status						Sum
	N0	N1	N2a	N2b	N2c	N3	
T1	21	2	0	0	0	0	23
T2	33	14	0	5	2	0	54
T3	3	4	0	2	4	0	13
T4	30	23	1	26	14	3	97
Sum	87	43	1	33	20	3	187

Informed consent was obtained from each patient before every treatment modality.

One hundred forty male (75%) and 47 female patients with a mean age of 59 ± 11 years (range, 38–88 years) were examined. Tumor sites were as follows: oral cavity (92%) and anterior oropharynx (8%). The oral cavity cancers consisted of 42% floor of mouth cancers, 21% tongue cancers, 13% cancers of the mandibular alveolar gingiva, 10% cancers of the soft palate and retromolar trigone, and 3% maxillary and cheek mucosal cancers. Distribution according to the Eastern Cooperative Oncology Group (ECOG) performance index was as follows: none, 65%; one, 21%; two, 12%; three, 1%; and four, 1%. Distribution by disease stage was as follows: stage I, 11%; stage II, 18%; stage III, 12%; and stage IV, 59%. Distribution by T classification and N status is shown in Table 1.

All patients received IA induction chemotherapy. Thirty-four patients received IA chemotherapy with 100 mg/m² cisplatin followed by an intravenous (IV) continuous infusion of 1 g/m² 5-fluorouracil for functional synergism (regimen A). The remaining 153 patients received IA chemotherapy with the high dose of 150 mg/m² cisplatin over 5 minutes in combination with parallel IV application of 9 g/m² sodium thiosulfate for systemic neutralization after a delay of 10 seconds (regimen B). Regimen A was abandoned because of relatively high toxicity. Toxicity of combined and monochemotherapy was noted according to the World Health Organization (WHO).¹⁴

On the morning of treatment, patients were given 74 mg of dolasetron and 75 mg of prednisolone IV. Afterward, 1.5 L of a full electrolyte solution (with 20 mval potassium chloride) was given by IV infusion over 2 hours. Catheterization of the right femoral artery was then performed using a size 4 French catheter containing a coaxial microcatheter. After superselective visualization of the tumor-feeding vessel by use of fluoroscopy and a contrast medium, either 100 mg/m² cisplatin dis-

solved in 500 mL 0.9% saline solution was infused IA over 1 hour (regimen A) or 150 mg/m² cisplatin dissolved in the same amount of saline solution was infused with controlled pressure (2 mL/s) (regimen B). For analgesia, 0.1 to 0.3 mg fentanyl was delivered intravenously (and on occasions 5–15 mg mepivacaine) into the perfused artery. With a delay of 10 seconds, an IV infusion of 9 g/m² sodium thiosulfate was given in parallel. After the treatment, 1 L of full electrolyte solution with 20 mval potassium chloride was infused intravenously over 5 hours. The next day, the patients were hyperhydrated with 3 L of a two-thirds electrolyte solution and were given thrombosis prophylaxis with heparin subcutaneously (SC) and, if necessary, dolasetron IV. Routine laboratory tests were performed on alternate days. The ward stay lasted between 4 and 6 days for most patients receiving regimen B. This time was prolonged by the 5-day continuous infusion of 5-fluorouracil (1 g/m²) for patients receiving regimen A. Daily application of allopurinol (300 mg) and antiemetic drugs was mandatory.

Three weeks after the first cycle, the local response to IA induction chemotherapy was assessed by visual inspection, palpation, and CT scan. A complete response (CR) was defined as complete clinical disappearance of the local tumor (radiologic volume 0% to 10% of volume at baseline). A partial response (PR) was a greater than 50% reduction in size of the tumor (radiologic volume 10% to 50% of volume at baseline). Progressive disease (PD) was a greater than 25% increase in size of the local tumor or appearance of new lesions (radiologic volume >125% of volume at baseline). Local tumor responses that did not meet any of the preceding definitions were designated as stable disease (SD). Unresectability defined as infiltration of the skull base, vertebra, or the carotid artery could not be converted to resectability because of this definition.

One hundred forty-four patients (77%) underwent surgery 3 to 4 weeks after chemotherapy. Surgery was omitted in 43 patients because of high comorbidity and local unresectability. The primary tumors were removed radically. In 85 patients (59% of surgical patients), bone resection had to be included (45 in-continuity resections of the mandible reconstructed with plates, 35 mandibular rim resections, and five maxillary resections). Fifty-three patients needed a temporary tracheotomy.

Surgical treatment was carried out according to the guidelines of the German-Austrian-Swiss

Cooperative Group on tumors of the maxillofacial region (DÖSAK),¹⁵ with two important modifications: if pretherapeutic staging including positron emission tomography (PET) resulted in the diagnosis of a clinically negative neck, only a suprahyoid neck dissection (SHND, a selective neck dissection that includes neck levels I and IIa) was carried out homolaterally, irrespective of the localization and size of the primary tumor. In case of a positive pretherapeutic finding on whichever side of the neck, a type III modified radical neck dissection (MRND) was carried out. If the histologic examination of the neck specimen revealed positive nodes despite a pretherapeutic N0 classification, an MRND of levels IIb, III, IV, and V was performed as early as possible. Beginning in March 2000, sentinel node dissection (SND) was performed instead of SHND in cases of clinical N0 status. In case of positive sentinel lymph nodes, an MRND was performed 1 week after SND. Radical neck dissections were carried out in cases of fixed lymph nodes.

The reconstructive measures were not disturbed by induction chemotherapy and were composed of myocutaneous flaps (35%), microsurgical free flaps (19%), local flaps (12%), and primary closure (27%).

One hundred twenty-four of the 187 patients (66%) underwent irradiation of the primary tumor and lymphatic drainage area, and 63 patients did not (34%). Thirty-eight of the latter 63 patients underwent surgery, but 25 patients were treated solely with local chemotherapy because of their poor general condition. Reasons for omission of radiation therapy were patient refusal, poor general condition, newly detected distant metastases, prolonged postoperative wound healing, psychiatric problems, earlier malignancies treated with radiation, and death. A commenced radiotherapy had to be aborted in only four cases (3%) (renal insufficiency, pneumonia, tumor waisting, heart failure). One hundred five of the 144 patients who underwent surgery (73%) underwent postoperative irradiation ($n = 24$) or postoperative chemoradiation ($n = 81$).

Before starting irradiation, patients were required to complete any dental procedures, including surgery and tooth extraction, and to demonstrate completely healed surgical wounds (interval surgery—radiation not more than 7 weeks to complete radiation within 100 days). All patients received a percutaneous endoscopic gastrostomy (PEG) tube to ensure sufficient nutrition during therapy. Mucositis prophylaxis included frequent rinsing of the mouth with dexamphenol

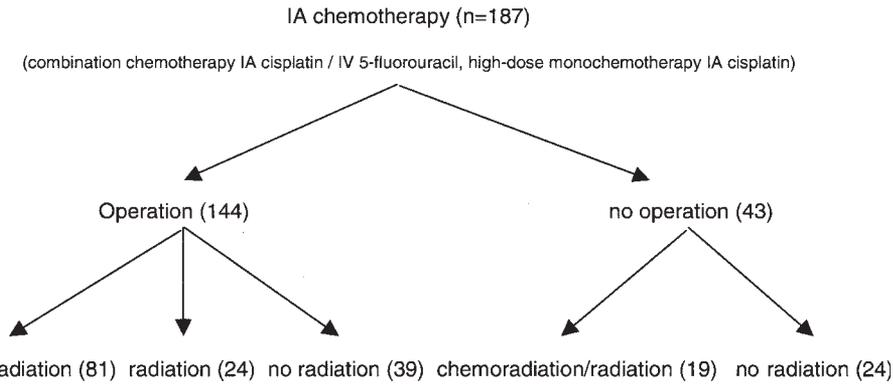


FIGURE 1. Complex multimodality treatment of an unselected consecutive patient population resulting in different treatment arms. Number of patients in brackets. IA, intraarterial; IV, intravenous.

and camomile tea. Patients were advised to maintain appropriate oral hygiene, use fluoride toothpaste, and abstain from alcohol and nicotine. Using thermal plastic masks for immobilization and three-dimensional planning (HELAX TMS) according to International Commission on Radiological Units and Measurements 50, radiotherapy was administered with a 6-MeV linear accelerator in daily fractions of 1.9 Gy on 5 days a week, to a total dose of 51.3 Gy. If the surgical margin was free, <0.1 mm or microscopic local tumor residues were detected, an additional boost of 10 Gy (22 patients) and 20 Gy (six patients) (5x/wk, 2.0 Gy/d) was delivered to these selected local areas,

respectively. The target volume was defined as the pretreatment tumor site and the bilateral regional lymph node areas including the submental, submandibular, pharyngeal, and retropharyngeal lymph nodes, as well as the lower cervical and supraclavicular regions, depending on tumor localization and stage. Because of the specific surgical procedure used in patients with T1–2 N0 tumors (suprahyoidal neck dissection), the lower neck was not irradiated in these patients. The target volume was treated with a rotating field technique combined with lateral and ventral portals using multileaf collimators. The allowed radiation dose to the spinal cord was 36 Gy.

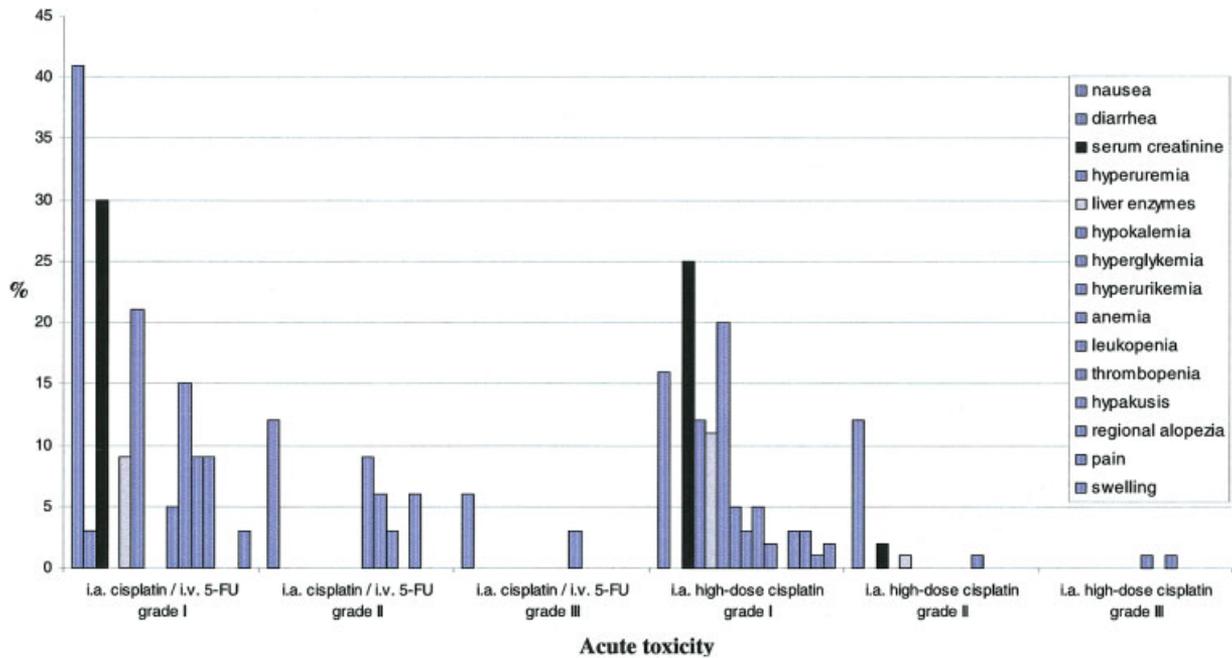
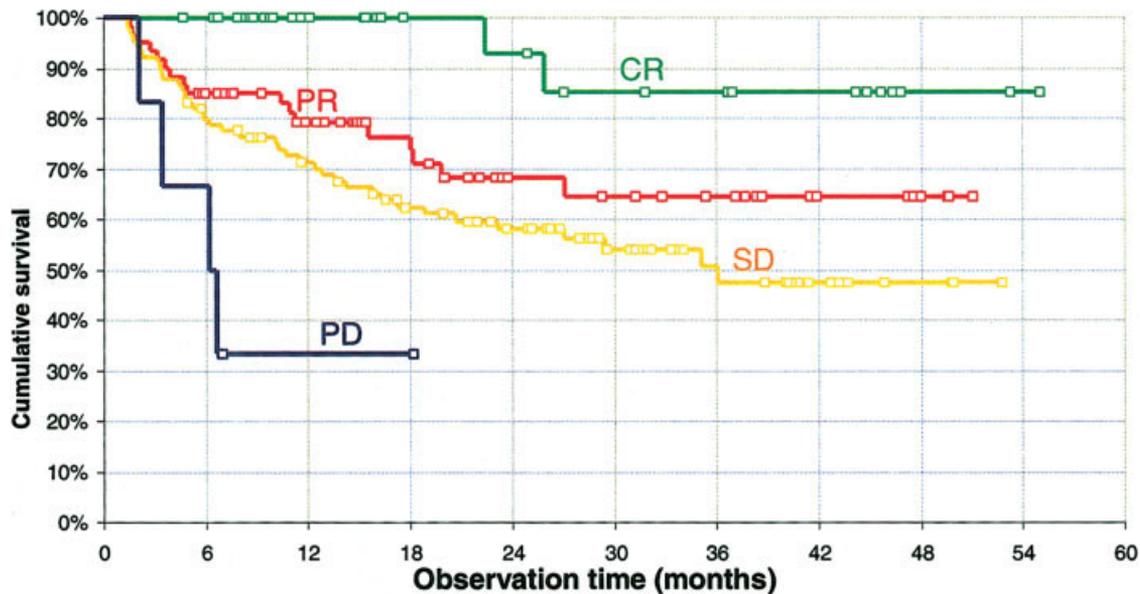


FIGURE 2. Toxicity according to World Health Organization¹⁴ of regimen A (intraarterial cisplatin followed by intravenous 5-fluorouracil) and regimen B (intraarterial high-dose cisplatin); 15% (regimen A) and 23% of patients (regimen B) had no measurable side effects, respectively. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



	Number of patients	Events	Number and percentage of patients alive	Cumulative 5-year survival
CR	32	2	30 / 94%	85%
PR	60	17	43 / 72%	64%
SD	89	39	50 / 56%	47%
PD	6	4	2 / 33%	33%
Sum	187	62	125	

FIGURE 3. Overall survival (Kaplan–Meier) compared with degree of response. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. Exploratory statistics (log-rank test) demonstrate significant differences between the curves of PR and CR (chi-square = 5.4, $p = .02$), of SD and CR (chi-square = 10.7, $p = .001$), of PD and CR (chi-square = 28.3, $p < .001$), of PD and PR (chi-square = 7.0, $p = .008$), and of PD and SD (chi-square = 4.4, $p = .04$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Eighty-six of the irradiated 124 patients (whether operated on or not) (69%) received concomitant systemic chemotherapy, and 38 (31%) did not. Reasons for omitting concomitant chemotherapy were patient refusal or contraindications such as liver disease or other internal diseases, advanced age, and poor general condition. Five patients had chemoradiation without surgery as organ-preserving treatment.

Concomitant chemotherapy was given on an inpatient basis. Docetaxel (Aventis Pharma S. A., Antony Cedex, France) was administered as an IV infusion over 60 minutes on day 2 of each weekly cycle of radiotherapy for a maximum of five cycles. Two different dose levels of docetaxel (20 and 25 mg/m²) were considered, with no difference in tolerability. To prevent edema and hypersensitivity reactions, the patients received oral dexametha-

sone 4 mg twice a day and oral cimetidine 300 mg daily for 3 days, starting the day before each administration of docetaxel. If a hypersensitivity reaction occurred, chemotherapy was stopped and prednisolone, 250 mg, and clemastine, 2 mg, were administered intravenously.

The median number of cycles of adjuvant postoperative chemoradiation administered in 81 patients was five (mean, 4.1 ± 1.3 cycles). Therapy was aborted in approximately 40% of cases, mainly because of grade III–IV oral mucositis. The mean number of administered cycles in patients with aborted chemoradiation was 2.5.

Because of this regimen, five different treatment arms were possible (Figure 1). The possible dependence or independence of local response to IA induction chemotherapy and ultimate treatment as carried out later was determined (by chi-

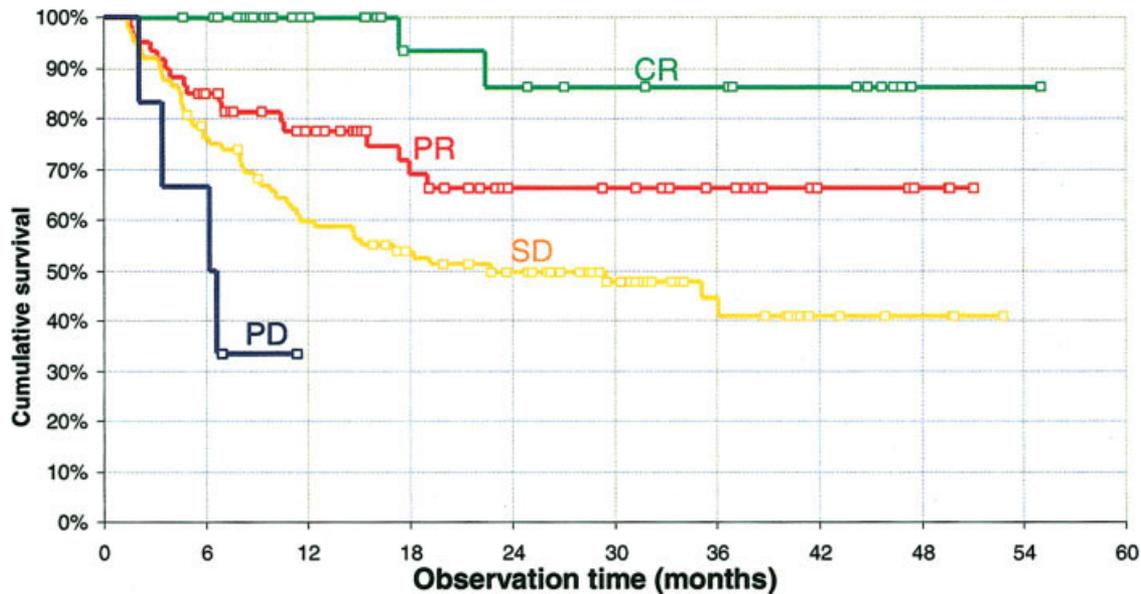


FIGURE 4. Disease-free survival (Kaplan–Meier) compared with degree of response. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. Explorative statistics (log-rank test) demonstrate significant differences between the curves of PR and CR (chi-square = 5.4, $p = .02$), of SD and CR (chi-square = 14.6, $p < .001$), of SD and PR (chi-square = 5.1, $p = .02$), of PD and CR (chi-square = 28.3, $p < .001$), and of PD and PR (chi-square = 7.7, $p = .005$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

square test). The toxicity of all modalities was recorded^{14,16} and has been published.^{7,11}

The correlation of local response after IA induction chemotherapy as assessed by clinical examination and CT scan was calculated by use of Spearman correlation coefficient. The overall and disease-free survival in relation to clinical local response after IA induction chemotherapy was calculated by use of the Kaplan–Meier method.¹⁷ Explorative statistical analysis was performed with the log-rank test. The 34 patients with additional systemic infusion of 5-fluorouracil were included because no statistical bias in the exclusive evaluation of local response was expected.

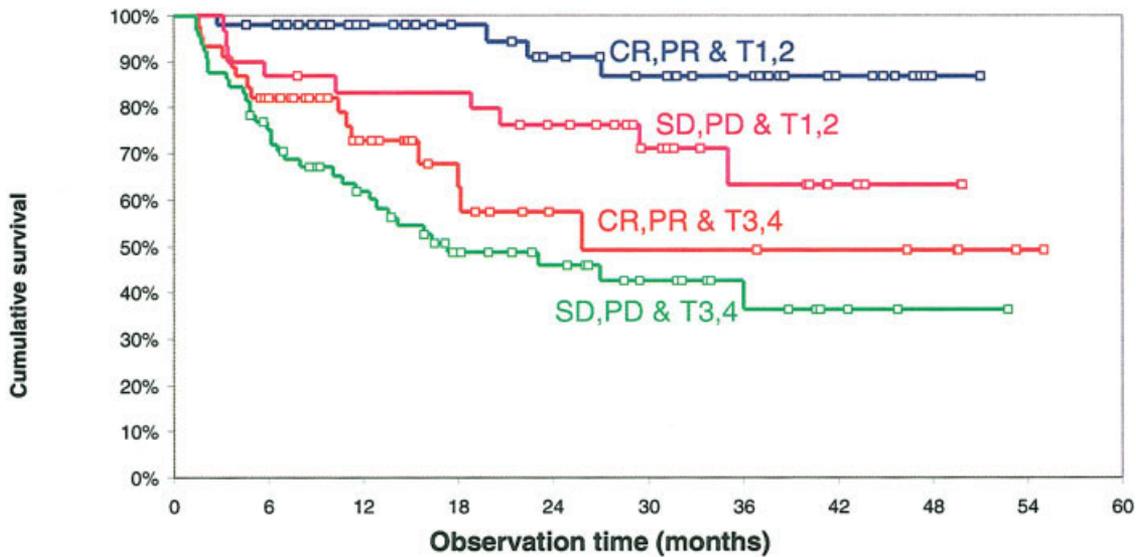
RESULTS

IA induction chemotherapy itself had very low acute side effects (Figure 2). Regimen A was aban-

doned because of more and higher grade I and II toxicity. IA high-dose cisplatin with systemic neutralization proved to be feasible.

Clinical and radiologic assessment of local response to IA chemotherapy had a statistically significant correlation ($r = 0.33$; $p < .001$). Therefore, local clinical response in patients with oral cancer could be assessed easily by visual inspection, and the more complicated radiologic volumetric evaluation was omitted for the statistical assessment of large populations. An individual prediction, however, was not possible because of the moderately high coefficient.

The overall survival rate of patients with CR of the primary tumor after neoadjuvant IA chemotherapy was significantly better than that of all patients with lesser response (explorative statistics). A PR did not offer a significant overall sur-



	Number of patients	Events	Number and percentage of patients alive	Cumulative 5-year-survival
CR,PR & T1,2	47	4	43 / 91%	87%
CR,PR & T3,4	45	15	30 / 67%	49%
SD,PD & T1,2	30	9	21 / 70%	63%
SD,PD & T3,4	65	34	31 / 48%	36%
Sum	187	62	125	

FIGURE 5. Overall survival (Kaplan–Meier) compared with degree of response with consideration of T classification. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. Exploratory statistics (log-rank test) demonstrate significant differences between the curves of CR, PR, and T3,4 and CR, PR, and T1,2 (chi-square = 13.8; $p < .001$), of SD, PD, and T1,2 and CR, PR, and T1,2 (chi-square = 4.3, $p = .04$), of SD, PD, and T3,4 and CR, PR, and T1,2 (chi-square = 24.1, $p < .001$), and of SD, PD, and T3,4 and SD, PD, and T1,2 (chi-square = 6.5, $p = .01$). It must be noted that survival is additionally strongly dependent of nodal status. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

vival benefit compared with SD. Local PD resulted in a statistically significant worse overall survival compared with all other groups (Figure 3).

For disease-free survival, the statistical differences in the curves between patients with clinical local CR, PR, and SD was significantly pronounced because of a worsening of disease-free survival of the patients with local SD (exploratory statistics); the curves for clinical local SD and PD did not differ significantly (Figure 4).

Consideration of T classification (Figure 5) proved a significant advantage for patients with small T1,2 tumors who had a positive response compared with the nonresponders (exploratory statistics). This result has to be emphasized, because small primary tumors do not develop lymph node metastases as often as locally advanced tumors do, and the effect of nodal dis-

ease on survival interfered with the assessment of the T classification. Consequently, the survival of the patients with advanced T3,4 tumors and positive response was not significantly worse than that of patients with small T1,2 tumors and SD or PD.

The evaluation of the nodal status (Figure 6) demonstrated an optical ranking of the survival curves according to the local response that was not entirely significant; this was most likely because the T classification that was not considered in this calculation.

Exploratory chi-square tests for the distribution of positive response in patients having diverse treatment combinations (eg, IA chemotherapy + operation + radiation vs IA chemotherapy + radiation) showed no significant differences except for the patients who underwent only local chemotherapy. These patients who could not be

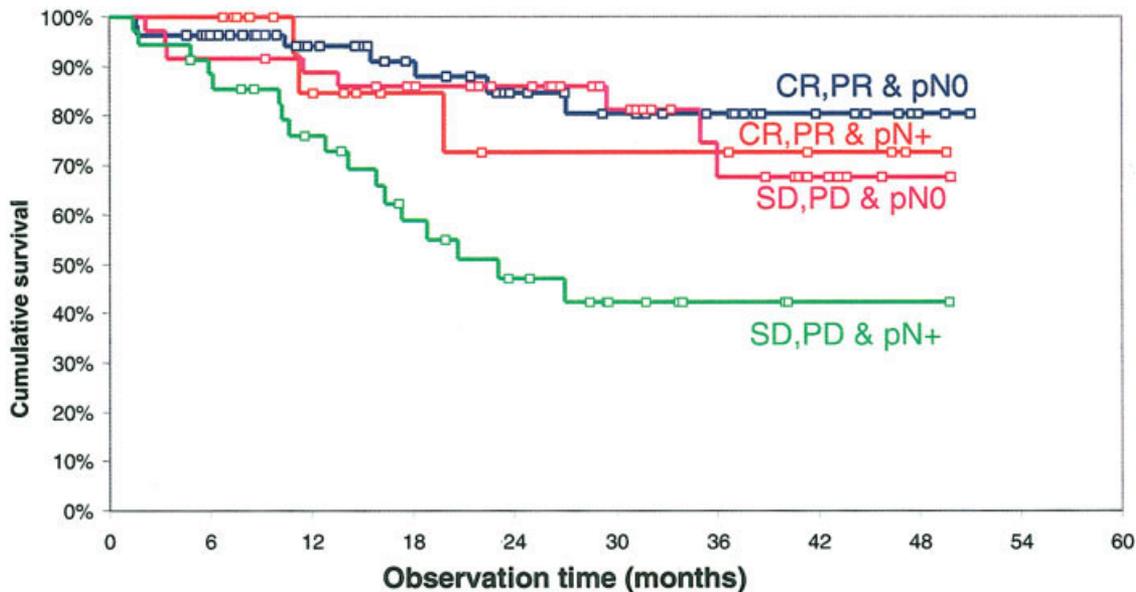


FIGURE 6. Overall survival (Kaplan–Meier) compared with degree of response with consideration of N classification. pN0, histopathologically free of nodal disease; pN+, histopathologic nodal disease. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. Exploratory statistics (log-rank test) demonstrate significant differences between the curves of SD, PD, and pN+ and CR, PR, and pN0 (chi-square = 11.8; $p < .001$), and of SD, PD, and pN+ and SD, PD, and pN0 (chi-square = 7.9, $p = .005$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

operated on and whose poor health precluded radiation had very far-advanced tumors. It could be concluded, therefore, that the formation of the treatment arms was not predisposed by the local response of the primary tumor.

The additional consideration of tumor stages (divided in the approximately equal groups of stages I, II, and III vs stage IV) did not result in significant differences (Figure 7). Although patients with lower-stage disease had generally higher rates of local remission, tumor stage did not significantly influence positive response to IA induction chemotherapy. Therefore, the general appraisal of local response as a strong prognostic parameter as shown in the Figures 3 and 4 can be maintained.

A combined assessment of stage, treatment, and local response to IA chemotherapy was carried out for stage IV and the most intensified treatment

with all modalities, because this subgroup consisted of a relatively large number of 44 patients. The Kaplan–Meier curves clearly differed between responders (19 patients) and nonresponders (25 patients) to IA chemotherapy (Figure 8).

DISCUSSION

Responders to systemic induction chemotherapy have a better general prognosis than nonresponders. Systemic chemotherapy has a possible local, regional, and systemic effect. IA chemotherapy has only a local effect, but, nevertheless, responders might have a better prognosis, too, thus revealing a tumor characteristic not known at baseline. Molinari et al¹⁸ used IA chemotherapy from 1971 to 1986. During this period, this modality was applied to 268 patients with various indi-

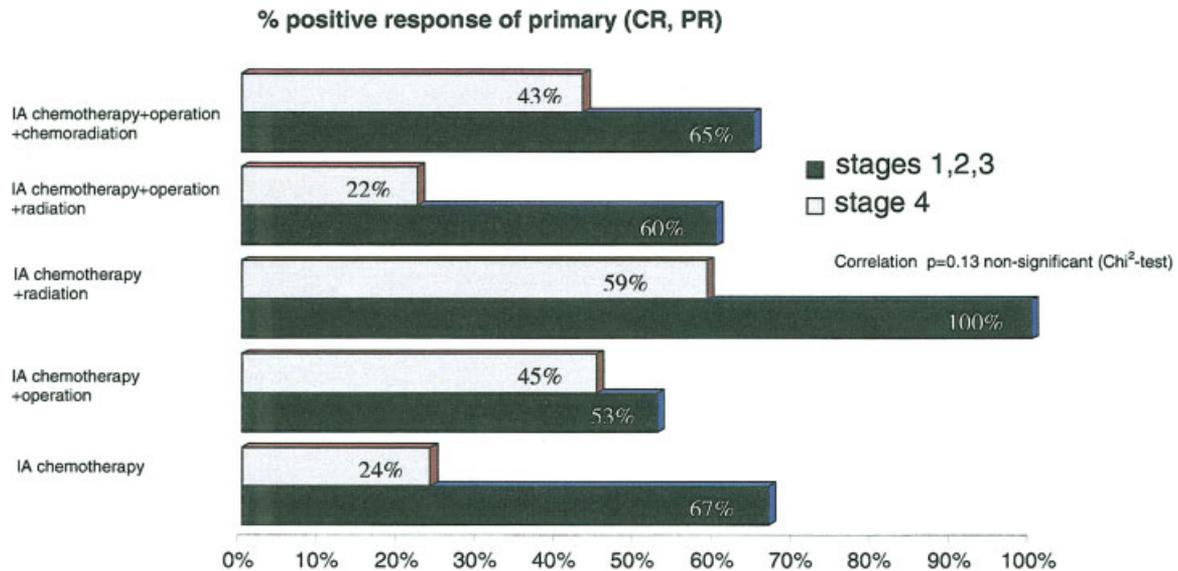
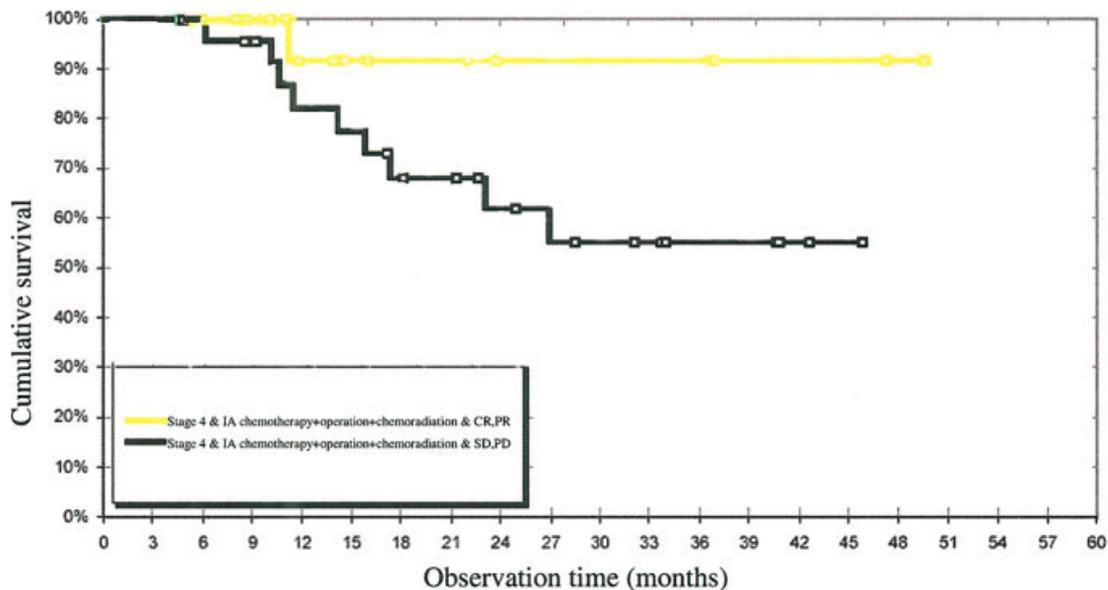


FIGURE 7. Frequency of positive response to induction chemotherapy compared with treatment arms correlated with stages. Population divided into stages 1, 2, 3 (41%), and stage 4 (59%). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

cations and various combinations of drugs through a catheter positioned in the external carotid artery after cannulation of the superficial temporal artery. The authors demonstrated that local recurrence rates were related to the initial

response to IA chemotherapy. This was clearly evident only in the case of remissions larger than 75% or complete remissions. The same was true for overall and disease-free survival. Response degrees lower than 75% (51% to 75% or lower than



	cases	died	without event	%	60 month survival probability
Stage 4 & IA chemotherapy + operation + chemoradiation & CR, PR	19	1	18	95%	92%
Stage 4 & IA chemotherapy + operation + chemoradiation & SD, PD	25	9	16	64%	55%

FIGURE 8. Combined assessment of stage 4, treatment arm, and local response to intraarterial chemotherapy. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

50%) were not statistically different but had a worse outcome compared with remissions larger than 75%. These findings were evident independent of the indication of IA chemotherapy for salvage of inoperable cases or planned in already operable ones.

Besides the various indications and drugs used in the mentioned study, IA chemotherapy over the temporal artery had several interventional drawbacks, such as cannulation failure, infection, catheter dislocation, lacking superselectivity, and others.¹⁸ IA chemotherapy is a very feasible method by modern femoral approach, angiographic technique, superselectivity because of microcatheters, and the use of high-dose cisplatin with peripheral neutralization. There could be many interesting consequences in case of a prognostic relevance of IA chemotherapy. It could be used (besides tumor induction and remission) as a diagnostic tool for stratification of further treatment.

The influence of T and N classifications, tumor stage, and therapy obscures the prognostic relevance of response to local chemotherapy. The results in the presented unselected population of 187 patients allow the conclusion that IA induction chemotherapy has a prognostic relevance for oral and oropharyngeal cancer, which is easily detectable by means of inspection and palpation of the local tumor 3 weeks after the intervention. This statement is independent of the various treatment combinations used, as demonstrated. On the contrary, even in the case of maximal treatment with all four modalities (IA chemotherapy, surgery, radiation, systemic chemotherapy), there was a possibility to demonstrate the prognostic relevance of IA induction chemotherapy. Tumor classifications and stages could well be integrated.

Hitherto, articles dealing with IA induction therapy simply reported the number of surviving patients with pathologic CRs without statistical analysis.⁴ Because local clinical response can easily be assessed by inspection in oral cancer, this parameter was examined. Other definitions of response, such as pathohistologic or radiologic response, would have been much more difficult to investigate. In the pathohistologic examination, correct diagnosis depends on the site of the biopsy and on the scrutiny of the pathologist. In radiologic examination, chemotoxic alterations of the tissue and edema can make correct evaluation difficult. The role of PET in such cases is not definitely established.¹⁹ Therefore, the value of clinical examination (inspection, palpation) after IA chemotherapy is increased by the prognostic relevance.

The very low rate of measurable acute toxicity of IA induction high-dose chemotherapy with cisplatin and systemic neutralization with sodium thiosulfate^{6,7,10-13} makes the routine use of this modality as screening tool for organ-preserving treatment options viable. First, cautious conclusions concerning a survival benefit of IA induction chemotherapy were drawn in a recent report.¹² The next logical steps would be prospective randomized studies with IA induction chemotherapy and molecular genetic investigations before and after this modality to learn about further characteristics of oral cancer.

Acknowledgments. I thank Ulrich Stefenelli and coworkers (Institute for Statistics, Würzburg, Germany) for carrying out the statistics.

REFERENCES

1. Schantz SP, Harrison LB, Forastiere AA. Tumors of the nasal cavity and paranasal sinuses, nasopharynx, oral cavity, and oropharynx. In: DeVita VT, Hellman S, Rosenberg SA, editors. *Cancer: principles & practice of oncology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2001. p 812.
2. Korogi Y, Hirai T, Nishimura R, et al. Superselective intraarterial infusion of cisplatin for squamous cell carcinoma of the mouth: preliminary clinical experience. *AJR Am J Roentgenol* 1995;165:1269-1272.
3. Hirai T, Korogi Y, Hamatake S, et al. Stages III and IV squamous cell carcinoma of the mouth: three-year experience with superselective intraarterial chemotherapy using cisplatin prior to definitive treatment. *Cardiovasc Intervent Radiol* 1999;22:201-205.
4. Benazzo M, Caracciolo G, Zappoli F, Bernardo G, Mira E. Induction chemotherapy by superselective intra-arterial high-dose carboplatin infusion for head and neck cancer. *Eur Arch Otorhinolaryngol* 2000;257:279-282.
5. Damascelli B, Patelli GL, Lanocita R, et al. A novel intra-arterial chemotherapy using paclitaxel in albumin nanoparticles to treat advanced squamous cell carcinoma of the tongue: preliminary findings. *AJR Am J Roentgenol* 2003; 181:253-260.
6. Kovács AF, Turowski B, Ghahremani MT, Loitz M. Intraarterial chemotherapy as neoadjuvant treatment of oral cancer. *J Craniomaxillofac Surg* 1999;27:302-307.
7. Kovács AF. Intraarterial chemotherapy and chemoembolization in head and neck cancer. Establishment as a neoadjuvant routine method. *Cancer Therapy* 2003;1:1-9 (<http://www.cancer-therapy.org/>).
8. Robbins KT, Storniolo AM, Kerber C, et al. Phase I study of highly selective supradose cisplatin infusions for advanced head and neck cancer. *J Clin Oncol* 1994;2: 2113-2120.
9. Robbins KT, Kumar P, Wong FS, et al. Targeted chemoradiation for advanced head and neck cancer: analysis of 213 patients. *Head Neck* 2000;22:687-693.
10. Kovács AF, Obitz P, Wagner M. Monocomponent chemoembolization in oral and oropharyngeal cancer using an aqueous crystal suspension of cisplatin. *Br J Cancer* 2002; 86:196-202.

11. Kovács AF. Mundhöhlen und Oropharynxkarzinome Neue Mittel und Wege der Therapie. Norderstedt: Books on Demand; 2003.
12. Kovács AF. Intra-arterial induction high-dose chemotherapy with cisplatin for oral and oropharyngeal cancer: long-term results. *Br J Cancer* 2004;90:1323–1328.
13. Tegeder I, Bräutigam L, Seegel M, et al. Cisplatin tumor concentrations after intra-arterial cisplatin infusion or embolization in patients with oral cancer. *Clin Pharmacol Ther* 2003;73:417–426.
14. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–214.
15. Bier J. Definitionen zum radikalchirurgischen Vorgehen bei Plattenepithelkarzinomen der Mundhöhle. Deutsch-Österreichisch-Schweizerischer Arbeitskreis für Tumoren im Kiefer und Gesichtsbereich (DÖSAK). *Dtsch Z Mund-Kiefer-GesichtsChir* 1982;6:369–372.
16. Seegenschmiedt MH. Interdisciplinary documentation of treatment side effects in oncology. Present status and perspectives. *Strahlenther Onkol* 1998;174(Suppl 3):S25–S29.
17. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
18. Molinari R, Chiesa F, Cantù G, Costa L, Grandi C, Sala L. Prognostic factors in cancer of the oral cavity and anterior oropharynx treated with preliminary neoadjuvant intra-arterial chemotherapy followed by surgery. In: Eckardt A, editor. *Intra-arterial chemotherapy in head and neck cancer—current results and future perspectives*. Reinbek: Eichhorn-Press Verlag; 1999. p 148–161.
19. Kitagawa Y, Nishizawa S, Sano K, et al. Prospective comparison of 18F-FDG PET with conventional imaging modalities (MRI, CT, and 67Ga scintigraphy) in assessment of combined intraarterial chemotherapy and radiotherapy for head and neck carcinoma. *J Nucl Med* 2003;44:198–206.