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Intraarterial chemotherapy and chemoembolization in head and neck cancer. Establishment as a neoadjuvant routine method

Research Article

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Summary

Over decades, local chemotherapy for head and neck cancer was a challenging treatment modality mainly for palliative use. In the last decade, a reappraisal started due to technical innovations. But a regular and safe clinical use has not been established, nor has a pharmacological rationale for this modality been given for humans. A routine intensification of effectivity by embolization in the region of the head and neck also had been a desideratum. In an unselected patient population of 213 patients suffering from oral and oropharyngeal cancer, the routine usage of intraarterial chemotherapy in a neoadjuvant pre-surgery setting could be demonstrated. Remissions, side effects and survival data are presented. In 88 of these patients, a novel dosage format of cisplatin and clear-cut indications enabled a safe routine execution of chemoembolization. By means of microdialysis, tumor and plasma concentrations of drugs involved could be measured in patients. The results presented prove the therapeutic advantage of intraarterial chemotherapy and, especially, of chemoembolization. The prognostic value of response to local chemotherapy is discussed. Intraarterial chemotherapy is an effective modality with low toxicity and should be used broadly in multi-modality regimens for head and neck cancer.

I. Introduction

Local chemotherapy as perfusion of drug solutions and as embolization by means of particles is mainly used for hepatocellular carcinoma and liver metastases of colorectal cancer (Tellez et al, 1998). This is safely possible because vessels are quite large in diameter, and metastases and liver tissue are nourished by different circulatory systems of the liver with consequent low risk to jeopardize healthy tissue (Breedis and Young, 1954). In the area of the head and neck, local chemotherapy, though used for decades, had many drawbacks, mainly caused by catheter complications and adverse effects due to flow-out of the antineoplastic agents (Molinari et al, 1999). Eleven percent failures of catheterization (mainly retrograde from the temporal artery into the external carotid artery), 8 % catheter dislocations, 15 % local inflammations, and 4-6 % neurological complications including head ache, apoplexias, and facial pareses made the method unattractive. Theoretically, as demonstrated in animal models (Harker and Stephens, 1992), the method nevertheless had the great advantage of higher tumor drug concentrations. Cisplatin proved to be the most effective drug (Harker, 1999) and gave the chance for rapid perfusion due to its relative cell phase non-specificity. Robbins transposed the so-called “two-route” chemotherapy (intraarterial cisplatin and its systemic neutralization by intravenous sodium thiosulfate) from the abdominal usage to the head and neck (Robbins et al, 1992). Modern sophisticated techniques like transfemoral catheterization, angiographic control, and superselective administration of a high dose of cisplatin (150mg/m^2 body surface) combined with peripheral neutralization reduced the complications and side-effects. The therapeutic approach was organ-preserving (combination with parallel radiation) or palliative.

The reported high effectivity and low systemic acute toxicity urged a broader usage of the method especially in consideration of the high mortality of head and neck cancer. Unselected populations of patients suffering from cancer of the oral cavity and the pharynx have a 5-year-survival of 40-45 % (Funk et al, 2002). Since 1996, intraarterial chemotherapy was used widely in a neoadjuvant pre-operative setting in the Department of Maxillofacial Plastic Surgery at Frankfurt am Main/Germany. The experimental and clinical results as well as novel developments of the method, leading to a routine usage of chemoperfusion and chemoembolization in the head and neck, are presented here.

II. Patients and methods

213 consecutive unselected patients with untreated primary squamous cell carcinoma of the oral cavity and the anterior oropharynx have been prospectively scheduled for treatment with neoadjuvant intraarterial chemotherapy and following surgery of the primary and the neck. Staging examinations encluded patient history, inspection, palpation, neck ultrasound, neck CT, chest X-ray, and "whole-body" PET. Patient and tumor data can be seen in **Table 1**. The methods for transfemoral catheterization and administration of the cisplatin solution, the cisplatin crystal suspension, and sodium thiosulfate are described in detail elsewhere (Kovács et al, 1999; Kovács et al, 2002a). Cisplatin as lyophilisate was produced by medac GmbH, Hamburg, Germany. At least one cycle was planned.

Three weeks later, dimension of response was assessed (CR=complete remission, a complete disappearance of local tumor mass; PR=partial remission, a partial reduction of local tumor mass of more than 50%; SD=stable disease, a partial reduction of local tumor mass of less than 50% or stability of local tumor mass; PD=progressive disease, growth of the tumor > 25%) and patients were scheduled to surgery. Surgery was executed according generally accepted rules (radical resection of the primary in healthy margins, ipsilateral modified radical neck dissection with preservation of the jugular vein, the sternocleidomastoid muscle and the accessory nerve in case of a clinically positive neck, contralateral selective neck dissection of the upper two levels of the neck in case of midline tumour location). Postoperative adjuvant treatment consisted in radiation or chemoradiation depending on the histological result, contra-indications for docetaxel, and patient agreement. Precise regimen is described elsewhere (Kovács et al, 2002b). Patients who could not be operated on have been offered a chemoradiation as organ-preserving treatment (71,3 Gy to the primary, 51,3 Gy to the neck, 5 cycles docetaxel 20 mg/m^2 body surface) or radiation (if there has been contra-indication for docetaxel).

Table 1

155 males, 58 females; average age: 60 yrs					
	cT	**cN**	**cM**	**cStage**	**pStage**
0		**107**	**208**		**22**
1	**25**	**51**	**5**	**24**	**35**
2	**62**			**38**	**22**
2a		**1**			
2b		**36**			
2c		**16**			
3	**20**	**2**		**30**	**24**
4	**106**				**68**
4A				**114**	
4B				**2**	
4C				**5**	
Sum	**213**	**213**	**213**	**213**	**171**

Demographic and tumor-related data of 213 unselected consecutive patients suffering from oral and oropharyngeal cancer. UICC classification: cT = clinical tumor category; cN = clinical node category; cM = clinical metastasis category; cStage = clinical staging; pStage = pathological staging.

During this study, it was planned to achieve a pharmacological rationale for intraarterial chemotherapy in humans. Tumor and plasma concentrations of cisplatin and sodium thiosulfate have been compared by means of microdialysis (Ungerstedt, 1991) in 10 and 6 patients with oral cancer treated either with intraarterial perfusion using a cisplatin solution (150 mg/m^2 in 500 ml 0.9% NaCl) or with embolization using a crystalline cisplatin suspension (150 mg/m^2 in 45-60 ml 0.9% NaCl), respectively. The microdialysis catheter was placed into the tumor (**Figure 1**), the intraarterial catheter into the tumor-feeding artery.

Cisplatin was rapidly administered through the intraarterial catheter and sodium thiosulfate (9 g/m^2) was infused intravenously. STS infusion was started 10 sec after starting the cisplatin infusion. Main advantage of the method is continuous measurement. Biopsies are not necessary. Further information can be found in Tegeder et al, 2003.

Primary endpoints have been local clinical and histological remission, and side-effects of chemoperfusion and chemoembolization, respectively. Secondary endpoints have been the establishment of a clinical routine chemoembolization method for cancer of the head and neck, and the survival analysis. End of follow-up has been January, 2003.

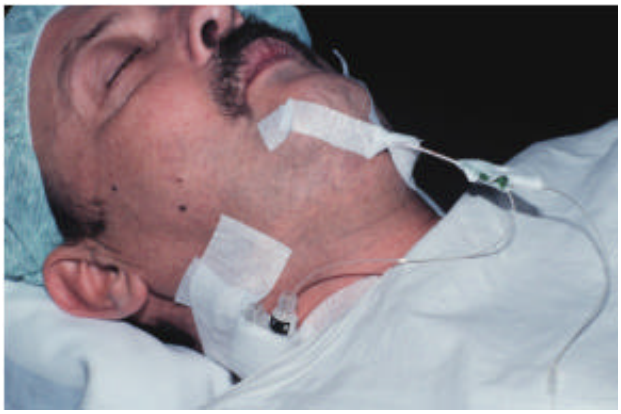

Figure 1: Patient suffering from cancer of the floor of the mouth lying on the angiography table. Microdialysis probe is placed via submental route into the tumor center. Tube (right) is perfusing the probe with saline solution, tube leading to vial fixed at the neck is saving the dialysate.

III. Results

All patients (100 %) received intraarterial chemotherapy. The therapy compliance has been excellent. In 32 patients, cycles have been repeated up to twice in case of non-operability and non-radiability, for palliative reason. There have been 256 interventions with 3 catheter-related complications (apoplexies, in two cases with complete remissions). Local remissions of the tumor after one cycle of intraarterial chemotherapy can be seen in **Figures 2A** (chemoperfusion) and **2B** (chemoembolization). Very low acute side-effects of both chemoperfusion and chemoembolization (mainly grade 1 WHO) are demonstrated in **Figure 3**. In the first 42 patients with 50 interventions of chemoembolization, there have been 3 temporary paralyses of the facial nerve and 4 facial skin necroses, both due to flow-out of cisplatin crystals into the medial meningeal artery (from the maxillary artery) or the skin collaterals of the tumor-feeding vessel. In the following 46 patients with 50 interventions, no such complications occurred. A containment of indications for chemoembolization has been the reason: safe procedure can be expected in the oral tongue, the floor of the mouth and the mandibular alveolar ridge (**Figure 4).** Preferential arteries for superselective catheterization have been the lingual and the facial arteries.

High-dose chemotherapy with cisplatin and systemic sodium thiosulfate can be used routinely in a neoadjuvant setting in the head and neck. Chemoembolization for oral cancer with cisplatin crystals is a safe routine method if administered in the mentioned localizations using the established method with cisplatin crystals.

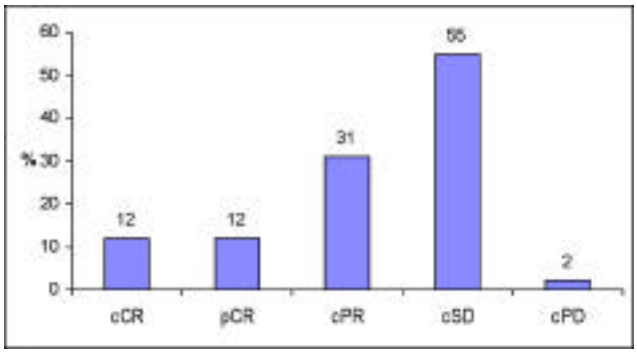

Fig. 2A: Clinical and histological response to intraarterial chemotherapy (chemoperfusion with cisplatin solution 150 mg/m^2 body surface) in 125 patients. cCR = clinical complete remission, pCR = pathological complete remission, PR = partial remission, SD = stable disease, PD = progressive disease. Overall response (cCR + cPR) = 43 %.

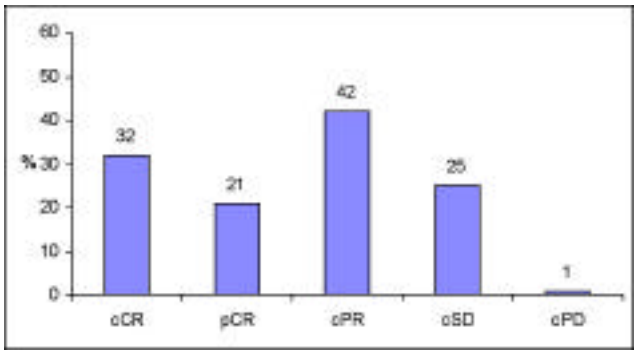

Figure 2B: Clinical and histological response to intraarterial chemotherapy (chemoembolization with cisplatin crystal suspension 150 mg/m^2 body surface) in 88 patients. Overall response = 74 %.

Hundred-seventy-one patients (80 %) have been operated on radically. Radicality of resections and postoperative complications were not influenced by pre-op chemotherapy. The neck surgery is listed in **Table 2**. Seven patients have not been operated on at the neck due to maxillary tumor location. Forty-two patients (20 %) could not be operated on due to non-resectability of the primary or due to bad general condition. 20 patients have been in such bad initial state that intraarterial chemotherapy was repeated as only treatment for local control. One of these patients (cT2cN0) is living free of tumor since 4 years now, the others died after a mean survival period of 4 months. 8 of these non-operated patients were in the condition to receive chemoradiation. In 4 patients, this organ-preserving treatment resulted in complete clinical remission of the detectable disease lasting for 13 months mean observation time. 14 patients without surgery received radiation therapy. These patients survived 3 months on average.

60 patients received no adjuvant treatment after surgery (small primaries, no histologic neck disease, refusals). 112 patients (53 %) underwent adjuvant radiation (n = 28) or adjuvant chemoradiation (n = 84). First results of adjuvant chemoradiation have been reported (Kovács et al, 2002b).

After a median observation time of 3 years (period from December 1996 to January 2003), 74 patients have died (35 %). 20 deaths have not been tumor-related. Kaplan-Meier-analysis generated a 5-year-survival expectation of 62 % but such estimations are solid only in case when 80 % of all patients reached the observation time of 5 years.

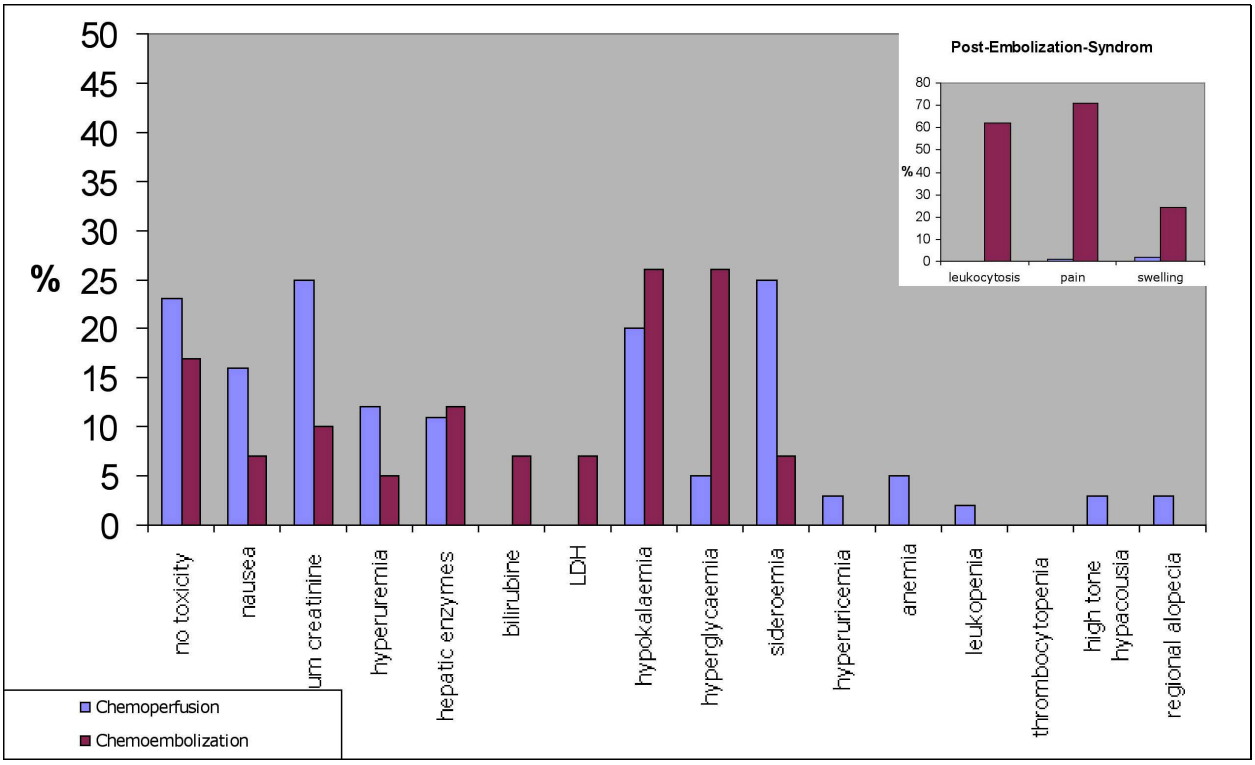

Fig. 3: Acute side-effects of chemoperfusion and chemoembolization (n = 213 patients). All grade 1 WHO normalizing after 5-7 days. Note high percentage of patients with no measurable side-effects at all. Chemoembolization has no hematological side-effects but causes post-embolization-syndrome which lasts 7-10 days.

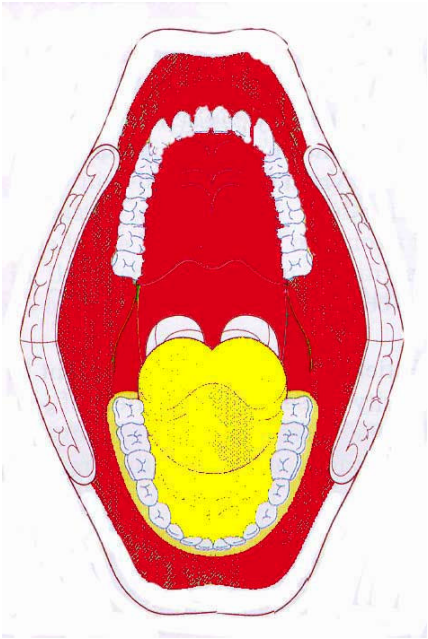

Fig. 4: Areas of safe chemoembolization with the cisplatin crystal suspension marked in yellow (oral tongue, floor of mouth, mandibular alveolar ridge).

Table II

RND	1
RND,MRND	1
MRND	27
MRND,MRND	10
MRND,SHND	38
MRND,SND	1
SHND	13
SHND,SHND	33
SHND,SND	1
SND	22
SND,SND	17
No neck surgery	7
Sum	**117**

Table 2: Neck surgery in 171 unselected consecutive patients with oral and oropharyngeal cancer (RND = radical neck dissection level 1-4; MRND = modified radical neck dissection level 1-4; SHND = suprahyoidal neck dissection level 1-2; SND = selective neck dissection [sentinel node biopsy]; MRND,SHND = ipsilateral modified radical neck dissection with contralateral suprahyoidal neck dissection, et cetera).

Following embolization, maximum cisplatin tumor concentrations and tumor-AUCs were about 5 times higher than those achieved after intraarterial perfusion with a cisplatin solution (maximum concentration: 180.3±62.3 µM versus 37.6±8.9 µM) whereas the opposite was true for plasma concentrations (maximum concentration: 0.9±0.2 µM versus 4.7±0.6 µM). Sodium thiosulfate plasma levels were about three times higher than its tumor concentrations (maximum tumor concentration 1685±151 µM; maximum plasma concentration 5051±381 µM). Following the standard intraarterial perfusion average sodium thiosulfate/cisplatin AUC ratios for tumor and plasma were 211±75 and 984±139, respectively. Following cisplatin embolization the respective ratios were 48.5±29.5 and 42966±26728 (**Figure 5**, Tegeder et al, 2003).

IV. Discussion

Intraarterial chemotherapy via transfemoral catheterization for advanced head and neck cancer was executed by several authors in a neoadjuvant pre-radiation setting (Vieitez et al, 1991; Scheel et al, 1996; Hirai et al, 1999) or as an organ-preserving method parallelly with radiation (Imai et al, 1995; Robbins et al, 1997; Oya and Ikemura, 1999; Regine et al, 2001). True neoadjuvant pre surgery usage of the method was very rare (Siegel et al, 1998; Benazzo et al, 2000).

In the Department of Maxillofacial Plastic Surgery at Frankfurt am Main/Germany, the "two-route" chemotherapy was used since 1996 for all tumor stages to improve overall survival of an unselected population (Kovács et al, 1999). The reported side-effects have been so low that broad usage of the method seemed to be feasible. The results after 256 interventions demonstrated a great technical safety of the method. Remissions have been high and side-effects very low (grade 1 WHO).

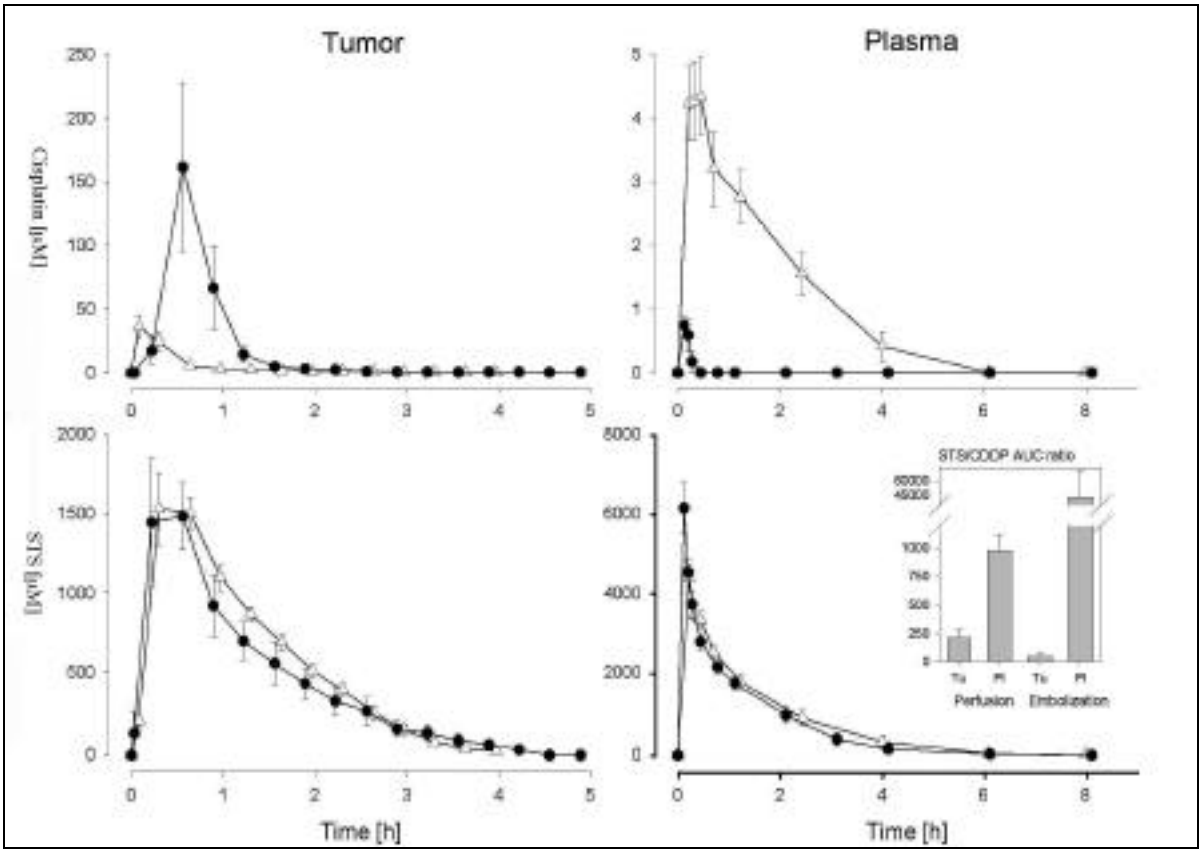

Figure 5: Mean ± s.e.m cisplatin (CDDP; top) and sodium thiosulfate (STS; bottom) concentrations in tumor tissue (left) and plasma (right) following superselective high dose intraarterial cisplatin perfusion (●) and crystalline cisplatin embolization (△). Note the different scaling of the y-axes for tumor and plasma.

Insert: Sodium thiosulfate/cisplatin AUC ratios for tumor and plasma following intraarterial cisplatin perfusion and cisplatin embolization (Tegeder et al, 2003).

The method was intensified by the usage of a new dosage format of cisplatin (crystal suspension) resulting in an embolization of the tumor bed (Kovács et al, 2002a). Embolization theoretically encreases the therapeutic advantage by a longer tumor residence time of the drug. The lyophilized cisplatin was reconstituted with 0.9% sodium chloride leading to a yellow mixture with a final concentration of 5 mg ml^{-1}. Microscopic assessment of the crystal diameters showed rod-shaped cisplatin crystals measuring 3x8 µm; regular clumping of these crystals formed particles measuring 30x50 µm. No extra embolizing particles have been necessary.

Embolization has been very rarely used in the head and neck area for cancer. Reports of other investigators are listed in **Table 3**. The fabrication of particles and encoating of the drugs was complicated and expensive, the head vessels having a small diameter have been occluded too early resulting in low doses of antineoplastic drugs, the danger of flow-out of stray emboli caused the investigators to stop the usage after a small number of patients. According to this body of literature, only 66 head and neck cancer patients have been treated with embolization regimens in the last 20 years all over the world. Effectivity has been not convincing. Side-effects have been neglected in these reports so far. The novel method of chemoembolization using a crystal suspension of cisplatin could be used routinely in 88 patients since May 2000 up to now. It was found to be very effective (remissions were evaluated following one cycle). Side-effects have been low, and early complications ceased after a confinement of indications to areas within the oral cavity. These areas harbor more than 60 % of the carcinomas of the oral cavity which guarantees a broad usage of this method.

Molar sodium thiosulfate/cisplatin ratios of >500 are required outside the tumor to neutralize cisplatin whereas tumor ratios should be <100 to avoid a loss of tumor cell killing (Abe et al, 1986, 1990). The first goal was achieved with both treatment modalities, the second only with cisplatin embolization suggesting that crystalline cisplatin embolization is superior to intraarterial cisplatin perfusion in terms of tumor cisplatin concentrations. This gave a definitive rationale for both intraarterial chemoperfusion as well as chemoembolization with a cisplatin crystal suspension in humans.

Overall compliance has been excellent. Intraarterial chemotherapy fits perfectly into a multimodality regimen as described. The survival of 65 % of an unselected population after a median observation time of 3 years must be considered as an improvement in overall survival which should be examined more precisely in a randomized study. Although administered locally and with local effect, the chemotherapy caused response has clear prognostic value (**Figure. 6**). The response apparently is dependent from the size of the primary tumor (**Figure. 7**), but even within the tumor classifications T1-2 and T3-4 there are differences in survival dependent from response (**Figure. 8**). Therefore, response to local chemotherapy can be used as prognostic sign. In contrast to other local treatment modalities like electroporation, photodynamic therapy or chemotherapeutic gel injections, intraarterial chemotherapy can be used in all tumor stages without side-effect limitations and is, therefore, best suited as a potential marker for differential therapeutic strategies. Potential subtypes of oral cavity squamous cell carcinomas may be found by more easily using a combination of intraarterial chemotherapy and gene expression analyses of the tumors.

Table III

Authors	Particles	Chemotherapeutics	Number of patients	Response	Side-effects
Okamoto et al, 1985, 1986	Ethyl cellulose microcapsules	Cisplatin 40 – 60 mg	11	63%	100% local pain
Kato et al, 1996	Ethyl cellulose microcapsules	diverse (mainly Cisplatin)	28 (incl. 11 of Okamoto et al)	28%	?
Tomura et al, 1996, 1998	Ethyl cellulose microcapsules	Carboplatin 100 mg	19	20%	60% local pain
Li et al, 1999	Albumine microspheres	Cisplatin 13,6 mg	7	?	?
Suvorova et al, 2002	Coil fragments	5-Fluorouracil 700 mg/m^2 + Methotrexat 40 mg/m^2	12	58%	?

Table 3: List of other reported chemoembolizations for cancer in the head and neck area. Note low dosage of drugs and small patient populations.

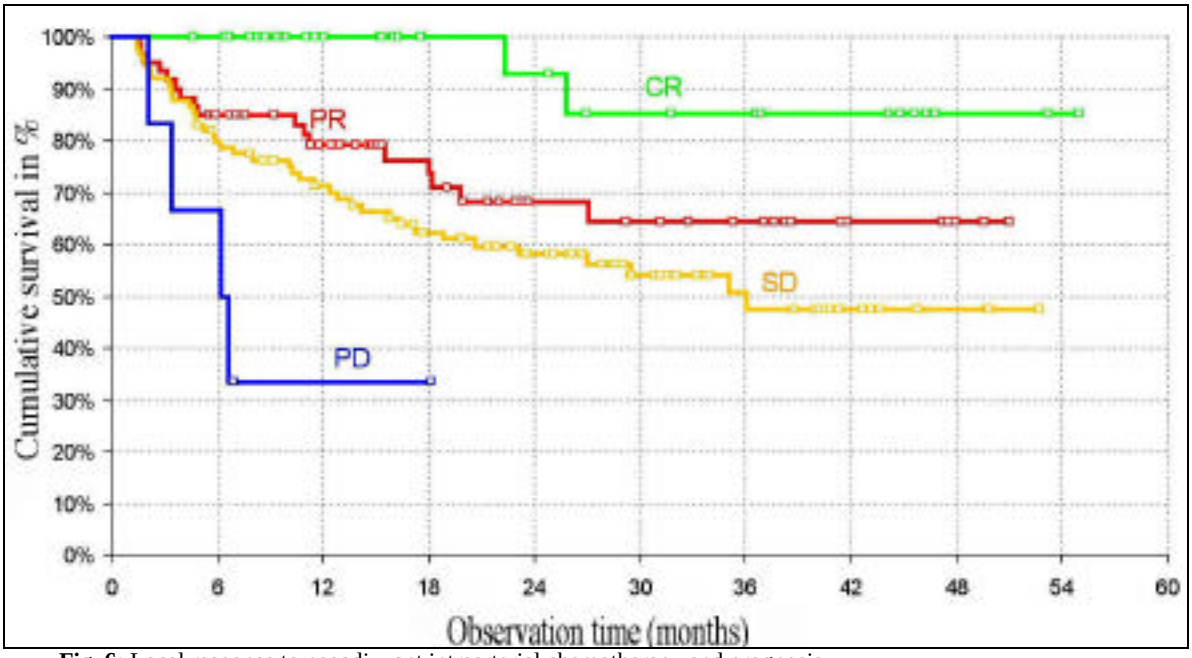

Fig. 6: Local response to neoadjuvant intraarterial chemotherapy and prognosis.

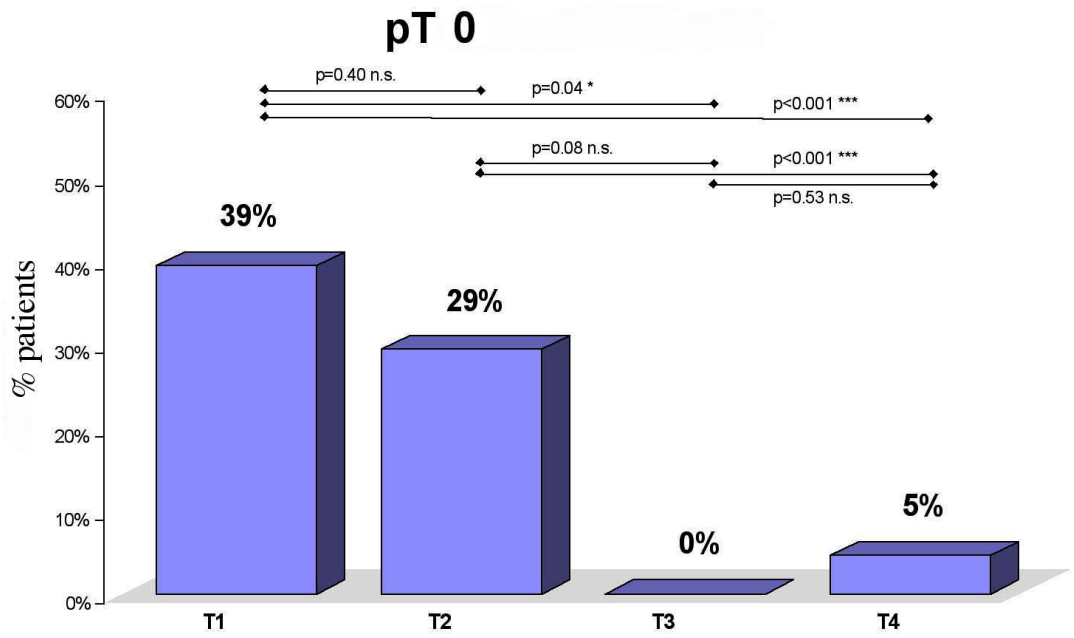

Fig. 7: Histological complete local remission (pT0) to neoadjuvant intraarterial chemotherapy in relation to local tumor classification. N. s. = non significant, *** = highly significant (Chi-square-test).

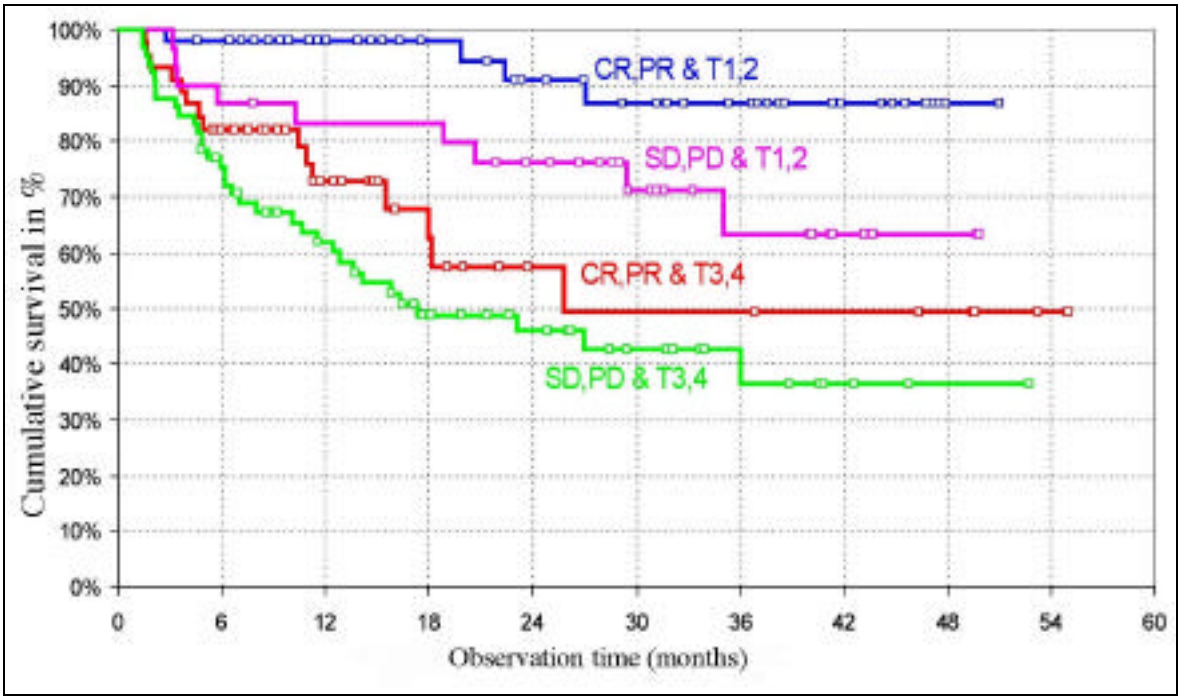

Fig. 8: Prognostic influence of local response within "small" (T1-2) and "advanced" (T3-4) local tumor classifications.

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