CHEMOEMBOLIZATION OF ORAL CANCER-ANALYSIS OF 100 CONSECUTIVE PATIENTS

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Abstract

Chemoembolization for cancer in the head and neck is a challenge. Due to local characteristics and risks, it was used very rarely in the past. By the combination of antineoplastic activity and embolizing effect in the same pharmacon, a routine usage seemed to be possible. A cisplatin suspension in normal saline (5 mg in 1 ml) with precipitation of microembolizing cisplatin crystals and without additional pharmacons was prepared. Cisplatin dosage was 150 mg/m^2, maximum absolute dose 300 mg, maximum amount of fluid 60 ml. Hundred consecutive patients with previously untreated squamous cell carcinomas of the oral cavity and the anterior oropharynx could be treated in a neoadjuvant setting with superselective chemoembolization using the cisplatin suspension. Compliance has been excellent. Overall response (CR + PR) after one cycle has been 73%, with 18.5% pathological complete remissions. Measurable acute systemic toxicity has been very low (grade I WHO). Post-embolization syndrome, especially swelling, had to be observed carefully. There have been 3.5% interventional and 9% local complications. These complications could be significantly reduced when chemoembolization was executed only in cancers of the oral tongue, the floor of the mouth, and the mandibular alveolar ridge. As a conclusion, chemoembolization in the head and neck area can be carried out routinely and safely using this method, and is highly effective. High local and low systemic cisplatin dose could be confirmed pharmacologically. Further investigation is mandatory to assess potential in local control and survival.

Key words
Chemoembolization, head and neck cancer, cisplatin, neoadjuvant therapy

QUIMIOEMBOLIZACION DEL CANCER ORAL: ANALISIS DE 100 PACIENTES CONSECUTIVOS

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Resumen
La quimioembolización para el cáncer de cabeza y cuello es un desafío. Debido a las características y riesgos locales fue utilizada raramente en el pasado. La combinación de actividad antineoplásica y efecto embolizante en el mismo fármaco puede hacer posible su uso rutinario. Se preparó una suspensión de cisplatino en solución salina normal (5 mg en 1 ml) con precipitación de cristales de cisplatino microembolizantes. La dosis de cisplatino fue de 150 mg/m^2, dosis máxima absoluta 300 mg, máxima cantidad de líquido 60 ml. Se trataron cien pacientes consecutivos con carcinomas de células escamosas de la cavidad oral y orofaringe anterior, sin tratamientos previos con terapia neoadyuvante, con quimioembolización superselectiva con la suspensión de cisplatino. La aceptación fue excelente. La respuesta conjunta (remisión completa más remisión parcial) después de un ciclo fue del 73% con 18.5% de remisión completa anatomopatológica. La toxicidad sistémica aguda cuantificable fue muy baja (grado I de OMS). El síndrome posembolización, especialmente tumefacción, se pesquisó cuidadosamente. Hubo 3.5% de complicaciones relacionadas con la intervención y 9% locales. Estas complicaciones pudieron reducirse significativamente cuando se efectuó la quimioembolización sólo en las neoplasias de la lengua, piso de la boca y borde alveolar mandibular. En conclusión, con este método es posible llevar a cabo la quimioembolización en el área de la cabeza y cuello en forma segura y de rutina, con elevada eficacia. Las dosis altas y bajas de cisplatino sistémico pueden ser confirmadas farmacológicamente. Es necesario la realización de mayores investigaciones para valorar el control local y la sobrevida.

Palabras clave
Quimioembolización, cáncer de cabeza y cuello, terapia neoadyuvante con cisplatino

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Full Text

CHEMOEMBOLIZATION OF ORAL CANCER-ANALYSIS OF 100 CONSECUTIVE PATIENTS

Introduction

Chemoembolization is mainly used for hepatocellular carcinoma and liver metastases of colorectal cancer[1] with high effect. The rationale is

increasing the regional advantage by reduction or stop of blood flow using microcapsules[2] or embolizing agents[3] resulting in longer tumour residence time, enhancement of first-pass extraction of the drug, and also hypoxic necrosis which is intended. Embolization with encoated drug microcapsules or mixtures of drugs and embolizing agents is safely possible because liver vessels are quite large in diameter, have a high flow, and metastases and liver tissue are nourished by different circulatory systems of the liver with consequent low risk to jeopardize healthy tissue.[4] Besides the drawback of a complicated technical production of embolizing agents, there are extreme obstacles concerning this method of a complete temporary halt of blood flow in the head and neck area: intolerable local necrosis and danger to eyes and nerve ganglions via anastomoses. Due to these facts, use of chemoembolization was casual in the head and neck region to date.

Even without embolizing agents, local chemotherapy, though used for decades, had many drawbacks in the area of the head and neck, mainly caused by catheter complications and adverse effects due to flow-out of the antineoplastic agents.[5] 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 intraarterial chemotherapy unattractive. Theoretically, as demonstrated in animal models,[6] the method nevertheless had the great advantage of higher tumor drug concentrations. Cisplatin proved to be the most effective drug[7] and gave the chance for rapid perfusion due to its relative cell phase non-specificity. Robbins and co-workers 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.[8] Modern sophisticated techniques like transfemoral catheterisation with small catheter systems, angiographic control, and superselective administration of a high dose of cisplatin (150 mg/m^2 body surface) combined with peripheral neutralization reduced the complications and side-effects. By these methods, plasma clearance is increased and drug targeting becomes still higher. Sensitive compartments, such as the bone marrow, gut, and kidneys are protected from the toxic effect of the drug. The lingual or facial artery being small vessels have a low flow (about 120 ml/min) which additionally raises drug targeting. The therapeutic approach was organ-preserving (combination with parallel radiation) or palliative.

The reported high effectivity and low systemic acute toxicity of local intraarterial chemotherapy urged a broader usage of the method especially in consideration of the high mortality of head and neck cancer which is caused mainly by local relapses. Therefore, a treatment modality concentrating on the local problem is of high interest in that disease. Since 1996, intraarterial chemotherapy was used widely (over 250 patients) in a neoadjuvant pre-operative setting in the Department of Maxillofacial Plastic Surgery at Frankfurt am Main/Germany.[9-13] Systemic and local toxicity could be reduced to nearly zero.

Since 2000, a dosage format of cisplatin was introduced combining the advantages described above (high dose, chemoembolization, high response, low toxicity, use of antagonist) without the drawbacks.[12-15] The experimental and clinical results of this novel development, leading to a routine usage of chemoembolization in 100 patients with cancer of the head and neck, are presented here.

Patients and methods

Patients and study design

100 consecutive patients with histologically proven, previously untreated primary SCC of the oral cavity and the anterior oropharynx have been

prospectively scheduled for treatment with neoadjuvant intraarterial chemoembolization (males/females ratio = 69/31; mean age: 60.5 years; performance status according to ECOG[16] 0/41, 1/44, 2/15; grading II/90, III/10). Distribution of clinical tumour sizes (cT), clinical regional lymph node classification (cN), and clinical stages (cSt) according to UICC[17] were noted (figures 1 - 3). Tumor sites have been the floor of the mouth (40%), the oral tongue (27%), the soft palate (13%), the gingiva of the mandibular alveolar process (12%), the lower vestibular sulcus (4%), the retromolar trigone (2%), and the maxillary gingiva and the lip (each 1%). 43% of tumors involved the midline. Staging examinations encluded patient history, inspection, palpation, neck ultrasound, neck CT, chest X-ray, and "whole-body" PET. Positron emission tomography was decisive for neck staging. Ethical approval was given by the local ethical committee. Informed consent was obtained prior to the onset of chemotherapy and all other therapeutic procedures (e.g.: operation, chemoradiation). The only exclusion criterion was the presentation of a heavy renal insufficiency.

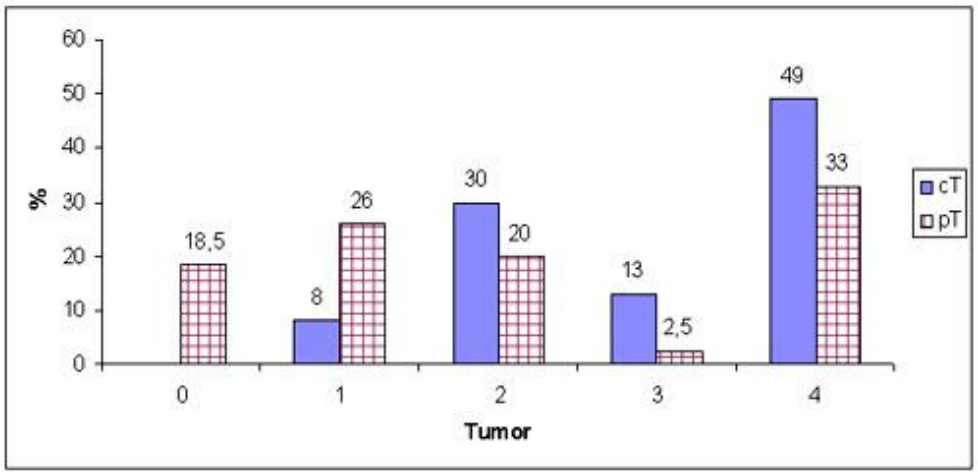

Figure 1. Clinical (cT) and pathological (pT) tumor classification in 100 patients treated with chemoembolization and 81 patients operated on.

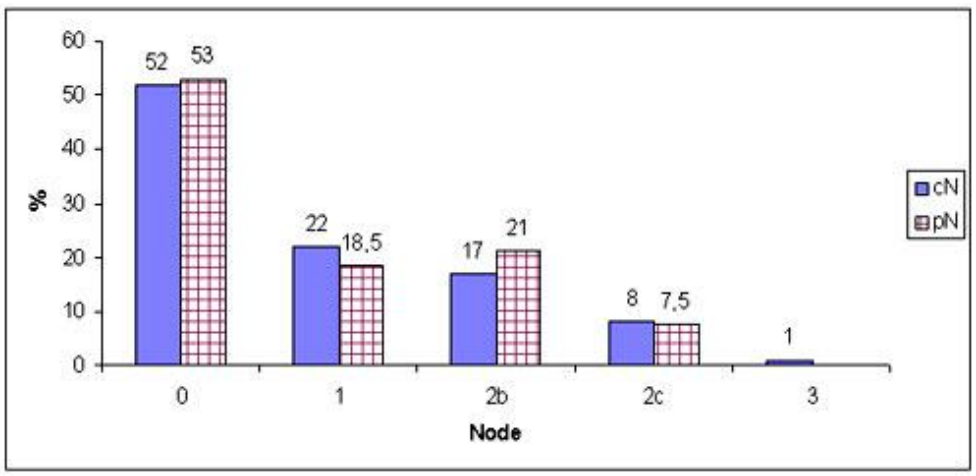

Figure 2. Clinical (cN) and pathological (pN) regional nodal classification in 100 patients treated with chemoembolization and 81 patients operated on.

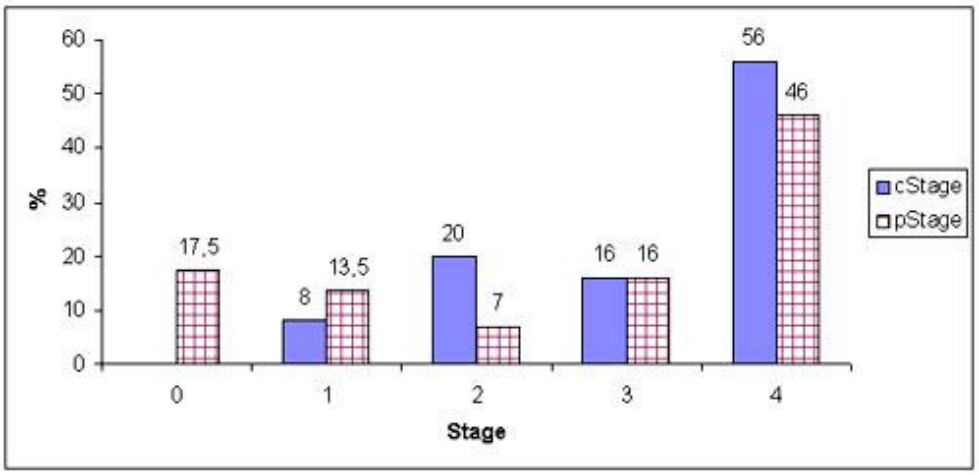

Figure 3. Clinical (cStage) and pathological (pStage) staging in 100 patients treated with chemoembolization and 81 patients operated on.

Preparation of an aqueous crystal suspension of cisplatin for intra-arterial application

Cisplatin (medac GmbH, Hamburg, Germany) is available in brown glass vials containing a sterile yellowish-white lyophilized powder with 50 mg cisplatin (pharmacon), 450 mg sodium chloride, 500 mg mannitol and hydrochloric acid (adjuncts). The individual patient dosage is 150 mg/m^2.[18] Body surface is calculated by the empirical formula of Du Bois,[19] limited to a value of 2 m^2 referring to 300 mg cisplatin. The cisplatin suspensions were prepared individually at the centralized preparation area for cytotoxic drugs at the Department of Pharmacy at Johann Wolfgang Goethe-University Medical School. They were prepared under aseptic conditions using a vertical laminar airflow work bench (according to DIN 12950) as well as a weight controlled preparation software (Cypro 2.0, ars pharmaceutica Gesellschaft für klinisches Wissenschaftsmanagement und Softwarelösungen mbH, Hamburg, Germany). The lyophilized drug was reconstituted with 0.9% sodium chloride (Isotone Kochsalzlösung, Braun Melsungen AG, Melsungen, Germany) leading to a yellow 10 ml mixture with a final concentration of 5 mg/ml. The mixture was shaken until the powder was suspended without macroscopically visible clumps. The suspension of the needed number of vials was transferred with a cannula (18 G) into two 50 ml disposable sterile syringes (Perfusion Plastipak, Becton Dickinson, Heidelberg, Germany). The syringes were covered for light protection. Although physicochemical data for cisplatin solutions indicates a stability up to 28 days,[20] it was decided to set the maximal expiration time to 8 h at room temperature to limit non reproducible crystal growth. The ready-to-use syringes were labelled with the patients name, dosage, administration day, expiration time and the note "please shake before administration".

Pharmacological features of the aqueous crystal suspension of cisplatin

The preparation method results in a monocomponent, a highly concentrated aqueous suspension of cisplatin with recipitation of crystals. The physicochemical properties (e.g.: PtPt distances, molecular vibration analyses) of cisplatin crystals which did form in frozen solutions have been previously described elsewhere.[21] The stability of the cisplatin complex is pharmacologically assured in a suspension because sodium chloride is solved in a high concentration in this dosage format. The resulting fluid is a 5.4% sodium chloride solution. Hypertonic sodium chloride solutions reportedly do not have effect on pharmacokinetics of

cisplatin.[22] The osmolality is supposedly higher than in an aqueous solution (about 285 mOsm/kg)[23] but cannot be measured exactly because of the presence of crystalline precipitates. Theoretic osmolality of the described suspension as calculated approximately is 2 130 mOsm/kg. Microscopic assessment of particle diameters in the aqueous crystal suspension of cisplatin showed rod-shaped crystals measuring 3x8 µm; regular clumping of these crystals formed particles measuring 30x50 µm. Ratio of small to large particles was 100/1. In solutions where precipitates did form, redissolution occurred very slowly with warming back to room temperature.[24] At 40°C, the time of redissolution was about 20 to 30 min.[25]

Management of chemoembolization

At the day of intervention the patients received 74 mg dolasetron and 500 mg prednisolone i.v. in the morning. A 1.5 l dose of a full electrolyte solution (with 20 mval potassium chloride) was administered subsequently by i.v. infusion over 2 h. Transcutaneous catheterization of the right femoral artery was carried out subsequently using a 4-french catheter containing a coaxial micro-catheter. Superselective visualization of the tumour-feeding vessel and assessment of its volume capacity using fluoroscopy and a contrast medium were performed. It never has been necessary to perform a provocation test because angiography in these areas usually reveals enough information. Then, 150 mg/m^2 cisplatin (maximal absolute dose 300 mg, lowest dose 225 mg) suspended as mentioned above (maximal amount of fluid: 60 ml, smallest amount 45 ml) was infused with controlled pressure via a hand-held syringe. In all cases, stasis of flow inside the peripheral capillaries of the tumour could be noticed via fluoroscopy. For analgesia, 0.1 to 0.4 mg fentanyl and 1 to 2.5 mg droperidol were delivered i.v. before start of therapy. In cases of toothache, mainly observed during perfusion of the maxillary artery, 1 ml of a 1:10 diluted 1% lidocain-HCl injection into the perfused artery was able to block the pain. With a delay of 10 s, an i.v. infusion of 9 g/m^2 sodium thiosulphate was given in parallel. After the end of the chemoembolization no more sodium thiosulphate was given. Application of the cisplatin suspension was finished a maximum of 3 h after preparation. One thousand millilitres of full electrolyte solution with 20 mval potassium chloride was infused again (i.v. over 5 h, subsequent to treatment). Administration of 500 mg prednisolone i.v. was repeated in the late afternoon, with further repetition over a maximum of 3 days depending on local swelling. The day after intervention, the patients were hyperhydrated with 3 000 ml of a two-third electrolyte solution, received a thrombosis prophylaxis with heparin S.C. (and dolasetron i.v., if necessary). Routine analgesia was given with metamizol drops. Routine laboratory checks were made on alternate days and compared to pretherapeutic values. The side effects of the cycles according to WHO[26] were noted. It was decided to stop the study in case of grade III and IV toxicity. At least one cycle was planned. Three weeks later, dimension of local response was assessed was assessed clinically (by inspection and palpation) and by CT examination (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.

Because surgery was considered an important modality of treatment, complete remission was not necessarily aimed at. Regular repetitions of cycles striving at that aim seemed to be too straining for the patients who should undergo a multimodality treatment. The patients were scheduled

for surgery if they were fit for anesthesia or resection would not threaten vital organs. This judgement was carried out before the start of any treatment. The patients not treated by surgery were to undergo radiation or chemoradiation therapy. Surgery was executed according generally accepted rules (radical resection of the primary in healthy margins, ipsilateral modified radical neck dissection [MRND] with preservation of the jugular vein, the sternocleidomastoid muscle and the accessory nerve in case of a clinically positive neck, contralateral selective suprahyoid neck dissection [SHND] of the upper two levels of the neck in case of midline tumour location). Patients classified cN0 underwent sentinel node dissection (SND). 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.[11] 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).
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[27] 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 chemoembolization using the crystalline cisplatin suspension (150 mg/m^2 in 45-60 ml 0.9% NaCl), respectively. The microdialysis catheter was placed into the tumor via a submental route, 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.[28]
Endpoints have been clinical and histological remission, and side-effects of chemoembolization. End of follow-up has been December, 2003.

Results

Compliance

All patients (100 %) received one completed cycle of intraarterial chemoembolization. The therapy compliance has been excellent. Duration of injection at the end of neuroradiologic intervention was between 60 and 90 s. Toleration of chemoperfusion was good and the dosage of analgetics sufficient although patients reported of a short burning pain in the embolized area. In 12 patients, cycles have been repeated once in case of non-operability. Preferential arteries for superselective catheterization have been the lingual and the facial arteries (table 1). In the maxillary artery, embolization of the medial meningeal artery had to be avoided. This was accomplished by careful placement of the micro-catheter distally from the furcation.

Used artery	Number of patients
Lingual artery	53
Facial artery	20
Maxillary artery	11
Sublingual artery	5
Inferior alveolar artery	3
Mental artery	3
Deep lingual artery	2
External carotid artery	2
Occipital artery	1
Sum	100

Table 1. Arteries used for superselective catheterization and chemoembolization.

Interventional complications
There have been 112 interventions with 4 interventional complications (3.5%). Two patients suffered from apoplexies presumably caused by mobilization of atherosclerotic plaques by the catheter. Immediate lytic treatment resulted in complete remissions after several days in both cases. There have been two complications of transcutaneous femoral puncture: 6 days after intervention, a patient suffered from a scrotal haematoma, which was treated conservatively and experienced resorption after 15 days; one patient showed signs of embolism of the left leg at the day of intervention. For three years since, he had an aortofemoral prosthesis. Treatment with heparine was quickly successful.

Response
Local clinical remissions after one cycle of intraarterial chemoembolization can be seen in fig. 4. Overall response (CR + PR) after one cycle has been 73%. Fig. 1 demonstrates the effectivity of the method especially in T1-3 tumors. In T4 tumors, response was limited by bone involvement. 18.5% pathological complete remissions could be achieved after one cycle. Many of the pT1 tumors merely showed small tumor nests following chemoembolization. Fig. 2 demonstrates the superselectivity of the method: the nodal classification did not change following chemoembolization. Fig. 3 visualizes the concept of "downstaging". Due to the local effectivity of chemoembolization, mainly the smaller stages had a measurable benefit and the stages which depend from nodal classification (3 and 4) did not alter much. This statement, however, refers only to changes detectable by clinical and histological examination.

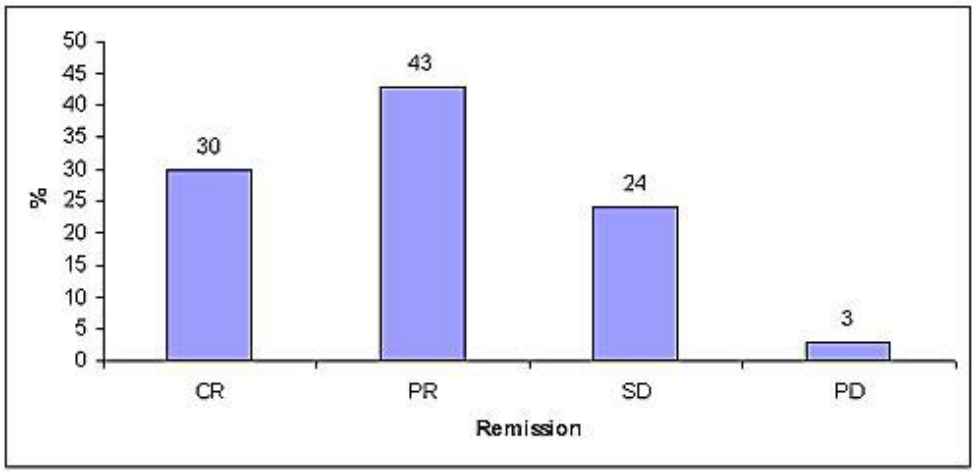

Figure 4. Clinical response in 100 patients after one cycle of chemoembolization. CR = complete remission, PR = partial remission, SD = stable disease, PD = progressive disease.

Acute toxicity

The very low acute systemic toxicity of chemoembolization (mainly grade 1 WHO) is demonstrated in figure 5. Slight hyperglycaemia up to 140 mg/dl vanished after 6 days. The local symptoms of pain and swelling combined with a nonfebrile leucocytosis (up to 19 000 mm^3) were similar to the known 'post-embolization syndrome'. Swelling of the cheek and the tongue was soft and vanished after 10 days. If swallowing was impaired, a gastric tube secured enteral nourishment. Moderate pain (grade II) was treated with metamizol and tramadol drops and, if painful superinfection in swollen epidermolytic areas of the oral mucosa was noticed, an oral antibiotic (clindamycine) was prescribed for 5 days. Leukocytosis was not treated and normalized after 10 days. Ward stay lasted between 3 and 17 days (mean: 9 days) which was necessary for financing this interventional procedure under the conditions of German hospital regulations. An observation on a ward is advisable for 3 days because swelling reaches its peak at that time point. Out-patient observation should generally be possible after that time.

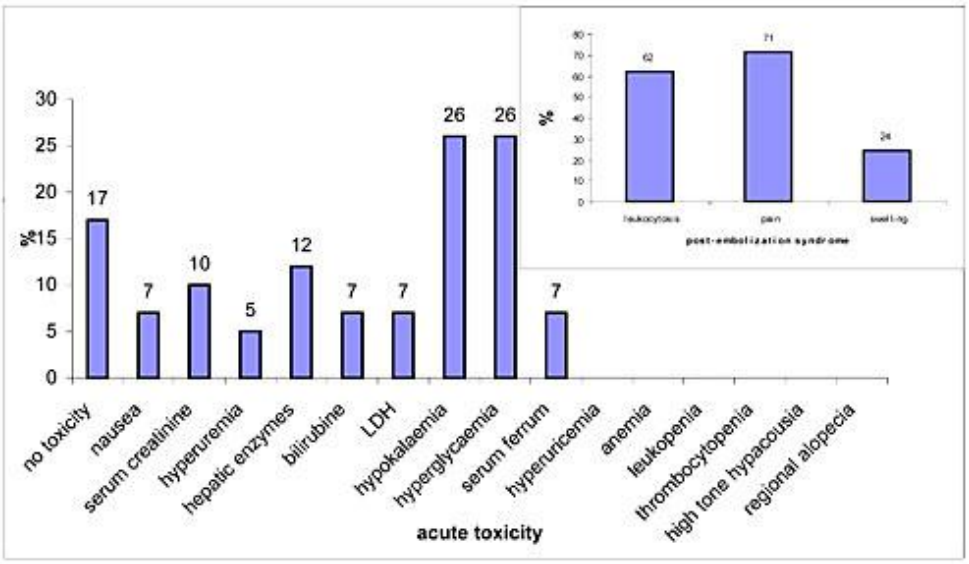

Figure 5. Acute toxicity measured in 100 patients after one cycle of chemoembolization.

Local complications

There have been 10 local complications (9%). In the first 49 patients with 58 interventions of chemoembolization, there have been 3 temporary paralyses of the facial nerve and 4 facial skin necroses (areas of the cheek and chin), 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. Recovery of nerve function took 3 months with small sequelae of the frontal branch. The skin necroses did not cause harm to the patients because these skin areas had to be resected during the operation in healthy margins. The flow-out could be expected in tumors of the retromolar trigone, the soft palate, and the maxilla where catheterization of the maxillary artery was necessary. Other complications have been 2 tracheotomies due to extreme swelling of the lower face, tongue, and neck on the second day after chemoembolization. The tube was removed after 3 days without difficulties and sequelae.
In the following 51 patients with 54 interventions, no such complications occurred except one tracheotomy of a very adipous woman whose moderate submental swelling was enough to cause dyspnea. In these patients, chemoembolization was carried out exclusively in tumors of the oral tongue, the floor of the mouth and the mandibular alveolar ridge where chemoembolization proved to be safe (figure 6). This means that the rate of complications could be decreased from 15% in the first half of patients to 2 % in the second half.

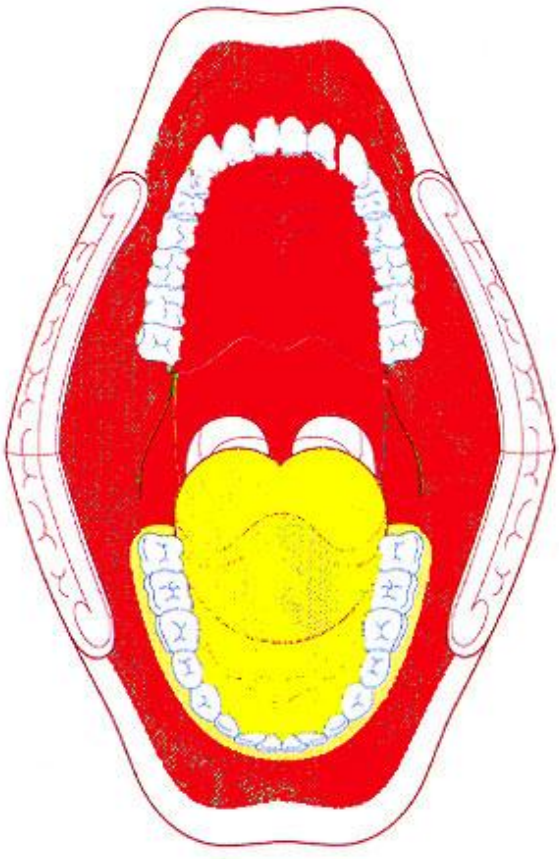

Figure 6. Areas of safe usage of chemoembolization: oral tongue, floor of mouth, mandibular alveolar ridge (yellow).

Further treatment and preliminary outcome
Eighty-one patients (81 %) have been operated on radically. Radicality of resections and postoperative complications were not influenced by pre-op chemotherapy. The neck surgery is listed in fig. 7. Nineteen patients (19 %) could not be operated on due to non-resectability of the primary or due to bad general condition. 6 patients have been in such bad initial state that intraarterial chemotherapy was repeated as only treatment for

local control. 13 non-operated patients were in the condition to receive radiation or chemoradiation.

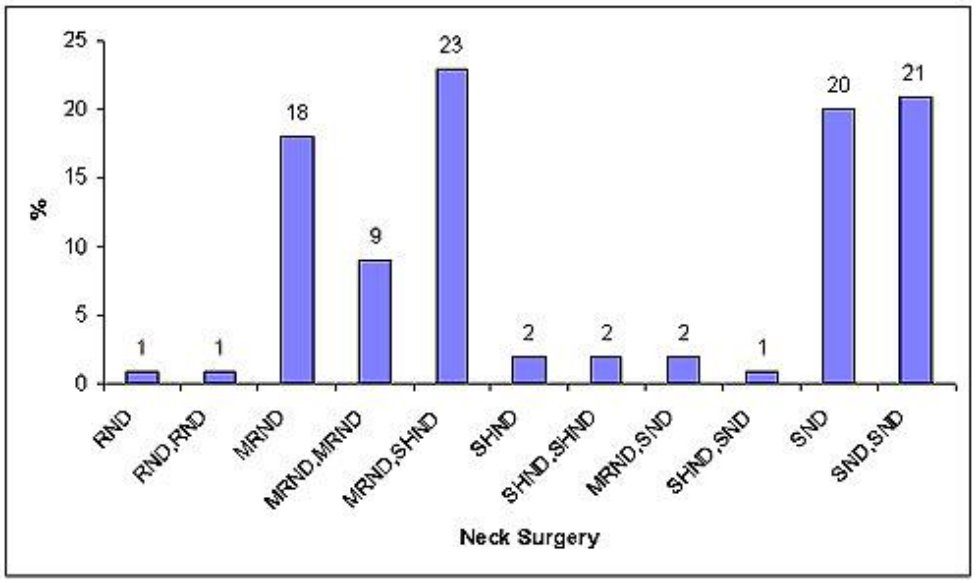

Figure 7. Distribution of neck surgery in 81 patients treated with chemoembolization. RND = radical neck dissection (ND), MRND = type III modified radical ND, SHND = suprahyoid ND, SND = sentinel node dissection; MRND,SHND = ipsilateral MRND and contralateral SHND and so on.

34 patients operated on received no adjuvant treatment after surgery (small primaries, no histologic neck disease, refusals). 47 patients underwent adjuvant radiation (n = 15) or adjuvant chemoradiation (n = 32). First results of adjuvant chemoradiation have been reported.[11]
In the period from May 2000 to December 2003, 36 patients have died (36 %). 12 deaths have not been tumor-related. There have been 13 local, 3 regional, and 7 distant relapses.

Cisplatin concentrations
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 42 966 ± 26 728.[28]
Discussion
Chemoembolization for cancer of the oral cavity and the oropharynx is a challenging but highly effective treatment modality. It is obvious that any embolizing agent would be extremely dangerous here. Anastomoses to the ophthalmic artery and arteries feeding nerval structures must not be occluded, not even a short time. Even a short complete occlusion of vessels like the facial or lingual artery would have the risk of necrosis of important tissue like the tongue or the cheek which would be intolerable, and painful. Swelling of the tongue base may cause suffocation. Furthermore, the amount of the embolizing agent cannot be completely assessed before the action of delivery because the exact diameter of the

perfused vessels and capillaries is not known and delivery has to be continued until occlusion is achieved. In the head and neck area, complete occlusion should be aimed at very cautiously. These are the reasons why chemoembolization was used rarely in the past.
Reports of other investigators are listed in table 2. The fabrication of particles and encoating of the drugs in these cases was complicated and expensive. The low doses of antineoplastic drugs have been the result of the small diameter of the head vessels which have been occluded too early. 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 77 head and neck cancer patients have been treated with embolization regimens in the last 20 years all over the world. Effectivity has not been convincing. Side-effects have been neglected in this reports so far.

Authors	Particles	Chemotherapeutics	Number of patients	Response	Side-effects
Okamoto et al, 1985, 1986 [18, 19]	Ethyl cellulose microcapsules	Cisplatin 40 – 60 mg	11	63%	100% local pain
Kato et al, 1996 [2]	Ethyl cellulose microcapsules	diverse (mainly Cisplatin)	28 (incl. 11 of Okamoto et al)	28%	not reported
Tomura et al, 1996, 1998 [20, 21]	Ethyl cellulose microcapsules	Carboplatin 100 mg	19	20%	60% local pain
Li et al, 1999 [22]	Albumine microspheres	Cisplatin 13,6 mg	7	?	not reported
Suvorova et al, 2002 [23]	Coil fragments	5-Fluorouracil 700 mg/m² + Methotrexat 40 mg/m²	12	58%	not reported
Song et al, 2002 [24]	?	?	11	?	?

Table 2. List of other reported chemoembolizations for cancer in the head and neck area. Note low dosage of drugs, small patient populations, and limited or lacking report of side-effects. Paper of Song et al. in Chinese, no further information available.

The novel method of chemoembolization using a crystal suspension of cisplatin could be used routinely in 100 patients since May 2000 up to now. It was found to be very effective (remissions were evaluated following one cycle). Systemic side-effects have been low, and early local 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. Usage is safe in these circumstances.
What is the novel idea of this method? To date, embolization was achieved either with encoated drugs (microcapsules)[2] or with concomitant delivery of embolizing substances like polyvinyl alcohol, lipiodol, albumine, degradable starch microspheres using mixtures, sometimes with several drugs.[1,36,37] These protocols have certain advantages: microcapsules provide good reproducibility of the product with good control of particle diameter, and a pharmacologically adjusted time of drug release. The embolizing substances occlude the tumour-feeding vessel for a certain time and stop intratumoural flow before being dissolved. These advantages compete with serious drawbacks: production of microcapsules is a complicated and expensive technical process, often necessitating 900% more encoating material than drug. The patient is stressed with additional substances which is also a drawback of the combination of several drugs (polychemotherapy) justified mainly in palliative treatment. In the case of auxiliary substances (it may be a viscous suspension like lipiodol or different larger microparticles), there is also the problem of production taking much costs, time, and effort. In contrast, the new technique presented has many principal advantages. It provides a monocomponent (cisplatin as made available by the producer) which serves as microembolizing agent

itself. This new dosage format of cisplatin (crystal suspension) combined both, antineoplastic and embolizing, effects in one agent.[15] For preparation of the infusion of a cisplatin solution, the manufacturer recommends diluting the cisplatin dose to a maximal concentration of 1 mg/ml.[20] At concentrations higher than 1 mg/ml precipitation of cisplatin occurs (suspension). The lyophilized cisplatin was reconstituted with 0.9% sodium chloride leading to a yellow mixture with a final concentration of 5 mg/ml. Microscopic assessment of the crystal diameters showed rod-shaped cisplatin crystals measuring 3x8 µm; regular clumping of these crystals formed particles measuring 30x50 µm which is ideal for head and neck vessels. No extra embolizing particles like degradable starch microspheres have been necessary. The demonstrated tumour response rate and the pharmacological results are clear indicators of better effect than achieved by a solution. It can be subsumed that the reason for this rate is not only the higher concentration of the drug in the suspension but the presumed slower intratumoural dissolution of the crystals.

Superselective administration of the agent into the tumour-feeding vessel is mandatory. Larger vessels normally cannot be occluded due to the particle diameters. Not only is the response better but the systemic acute toxicity is lower. This may have the following reasons. A higher intratumoural concentration resulting from a higher first-pass or trapping effect may be likely. A technical detail contributes to the favourable findings of higher response and less systemic toxicity. Intraarterial delivery of the smaller amount of fluid (maximum 60 ml aqueous cisplatin suspension) using a hand-held syringe results in better time management with consideration of the parallel intravenous infusion of sodium thiosulfate. The large amount of fluid used for the cisplatin solution (500 ml) sometimes led to spasms of the vessel and interruptions of perfusion. Duration of administration was longer (5 min), the pumps used provided a standardized flow but were clumsy in operation. Now the capacity of the vessel could be assessed by hand-controlled injection of saline first, followed by injection of the suspension with the same pressure. The injection could be executed quickly in less than 2 min without reflux of blood and possibly sodium thiosulphate, a good flow could be achieved with full exposure of the tumour bed to cisplatin. Sodium thiosulphate has reached the periphery when cisplatin arrived there.

The local side-effects could easily be overcome and posed no problems for maxillofacial routine care. Nevertheless, it must be stated that the method is dangerous if used in areas perfused by the maxillary artery. Local complications like facial paralyses or skin necroses can be avoided if the method is used in safe areas as shown in figure 6. In cases where such complications may be expected, the cisplatin solution should be used instead where no embolizing effect is present. The same is true for very obese patients.

There are no presently available multi-agent chemotherapies with comparable high local response rates after one cycle and similar low rates of acute side-effects. Overall compliance has been excellent. Intraarterial chemotherapy as neoadjuvant treatment fits perfectly into a multimodality regimen.[11] 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.

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.[38,39] Both goals were achieved with cisplatin embolization. This gave a definitive rationale for chemoembolization with a cisplatin crystal suspension in humans. Further investigation is mandatory to assess potential in local control and

survival.

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Autoevaluación

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