

Multimodality Treatment Including Postoperative Radiation and Concurrent Chemotherapy with Weekly Docetaxel is Feasible and Effective in Patients with Oral and Oropharyngeal Cancer

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Background: To examine the feasibility and efficacy of weekly docetaxel with concurrent radiation as postoperative treatment in a multimodality approach to oral and oropharyngeal cancer.

Patients and Methods: 94 patients (Table 1) with primary resectable squamous cell carcinoma of the oral cavity and oropharynx (UICC stage I 14%, II 15%, III 18%, IV 53%; Table 2) were treated with a multimodality therapy program consisting of neoadjuvant intra-arterial high-dose chemotherapy (cisplatin 150 mg/m² with parallel systemic sodium thiosulfate 9 g/m² for neutralization), followed by surgery of the primary and neck, and postoperative concurrent radiation and chemotherapy with weekly docetaxel (20–30 mg/m²; Table 3). Chronic toxicities were followed over a period of 5 years.

Results: At a median follow-up of 4 years, the 5-year survival rate for all 94 patients was 80%, and disease-free survival was 73% (Figures 1 and 2). Among patients with advanced disease (stage III and IV), survival was 83 and 59%, respectively (Figure 4). Grade 3 and 4 mucositis was the main acute toxicity necessitating supportive care. Long-term toxicity appears to be moderate (Table 4). The maximum tolerated dose of weekly docetaxel was 25 mg/m².

Conclusions: Concurrent radiation and chemotherapy with weekly docetaxel is a feasible postoperative treatment in a multimodality approach to oral and oropharyngeal cancer, resulting in high overall and disease-free survival. This approach warrants further evaluation in prospective randomized trials.

Key Words: Head and neck cancer · Docetaxel · Multimodal treatment · Adjuvant radiation

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Multimodale Therapie einschließlich postoperativer Bestrahlung und konkomitanter wöchentlicher Chemotherapie mit Docetaxel ist bei Patienten mit Mundhöhlen- und Oropharynxkarzinomen durchführbar und effektiv

Hintergrund: Untersuchung der Durchführbarkeit und Effektivität einer wöchentlichen Docetaxelapplikation bei konkomitanter Bestrahlung in einem multimodalen Behandlungskonzept von Mundhöhlen- und Oropharynxkarzinomen.

Patienten und Methoden: 94 Patienten (Tabelle 1) mit primären resektablen Plattenepithelkarzinomen der Mundhöhle und des Oropharynx (UICC-Stadium I 14%, II 15%, III 18%, IV 53%; Tabelle 2) wurden mit einem multimodalen Therapiekonzept behandelt, das aus einer neoadjuvanten intraarteriellen Hochdosischemotherapie (150 mg/m² Cisplatin mit paralleler systemischer Neutralisierung durch 9 g/m² Natriumthiosulfat), einer Radikaloperation des Primarius und des Halses sowie einer postoperativen konkomitanten Bestrahlung und Chemotherapie mit wöchentlicher Docetaxelgabe (20–30 mg/m²) bestand (Tabelle 3). Chronische Nebenwirkungen wurden über 5 Jahre hinweg beobachtet.

Ergebnisse: Nach einem medianen Follow-up von 4 Jahren lag die 5-Jahres-Überlebensrate aller 94 Patienten bei 80% und das krankheitsfreie Überleben bei 73% (Abbildungen 1 und 2). Bei Patienten mit fortgeschrittener Erkrankung (Stadium III und IV) lag das Überleben bei jeweils 83% und 59% (Abbildung 4). Eine Mukositis der Grade III und IV war die hauptsächlichste Akuttoxizität, die eine supportive Therapie nötig machte. Die Langzeittoxizität schien moderat zu sein (Tabelle 4). Die maximal tolerierte wöchentliche Docetaxeldosis war 25 mg/m².

Schlussfolgerungen: Die konkomitante Bestrahlung und Chemotherapie mit wöchentlicher Docetaxelgabe ist eine durchführbare postoperative Behandlung in einem multimodalen Therapiekonzept für Mundhöhlen- und Oropharynxkarzinome, die in einem hohen Gesamt- und krankheitsfreien Überleben resultiert. Dieser Therapieansatz erfordert eine weitere Bewertung in prospektiven randomisierten Studien.

Schlüsselwörter: Kopf-Hals-Karzinome · Docetaxel · Multimodale Therapie · Adjuvante Bestrahlung

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Introduction

Curative intent treatment for oral and oropharyngeal cancer involves radiation therapy, both as part of surgical or organ-preserving approaches. The combination of surgery and radiation therapy has been described as an “acceptable standard of care” in advanced stages of the disease [35]. Postoperative radiation therapy has been given priority to preoperative irradiation since Vandembrouck et al. [42] demonstrated lower morbidity and Tupchong et al. [41] observed a lower regional recurrence rate in the postoperative arm compared with neoadjuvant radiotherapy. A potential advantage of preoperative radiation is that it is directed at tissues not altered by scarring, but there are also clear drawbacks: wound healing may be impaired, and neoadjuvant radiation is given with a uniform dose irrespective of particular unfavourable factors becoming evident at the surgical specimen due to exact pathologic staging.

The benefit of chemotherapy added to locoregional treatment is well established [28]. It is also known that chemotherapy should be administered concomitantly with radiation therapy, while the cytotoxic agent best suited for chemoradiation is still under investigation. An ideal agent should be a potent radiosensitizer, and it should be reasonably well tolerated.

Taxanes are promising antineoplastic drugs. Docetaxel is a potent radiosensitizer *in vitro* [14, 30, 39] and has proven very effective in the treatment of non-small-cell lung cancer (NSCLC). For the treatment of advanced NSCLC and esophageal cancer, Mauer et al. [26] recommended weekly doses of 20 mg/m² of docetaxel given with concurrent radiation at a total dose of 60 Gy. However, the optimal dose for the treatment of other cancers including head and neck cancer is still not defined. In several studies, docetaxel was used at weekly doses between 15 mg/m² and 30 mg/m² with concomitant radiation up to 70 Gy [16, 21, 40]; these trials included patients with advanced inoperable tumors. In three phase II studies, docetaxel-based regimens given as induction therapy to patients with locally advanced squamous-cell carcinoma (SCC) of the head and neck yielded overall response rates from 93% to 100%, with complete response rates of 40% to 63% [29]. According to these studies, the combination of docetaxel with cisplatin and fluorouracil (TPF) seems to be the most effective regimen for response induction.

The present report describes the results of a phase II study of docetaxel given as part of a novel postoperative chemoradiation protocol for the curative treatment of head and neck cancer. Aggressive treatment of small tumors was justified by considering their prognosis; the tumor registry of the German-Austrian-Swiss Cooperative Group on tumors of the maxillofacial region (DÖSAK) does not support the opinion that stage I and II disease can be sufficiently treated with surgery alone (e.g. 75% only alive after 30 months for the surgically treated T1 tumors [17]). Furthermore, an overall improvement of results following oral anticancer therapy can only be achieved with tumors of smaller mass [44].

Patients and Methods

Eligibility Criteria

Consecutive patients with previously untreated, histologically proven, resectable SCC of the oral cavity or oropharynx were enrolled in the study. Patients with the following were excluded from the study: age > 80 years, known hypersensitivity to cisplatin or docetaxel, severely impaired renal or hepatic function (serum creatinine > 5 mg/dl as sign for a beginning renal insufficiency, serum bilirubin > 1.3 mg/dl and/or transaminases > 3.5 times the upper limit of normal), distant metastases or synchronous malignancies. Informed consent was obtained prior to every step of treatment, i.e., preoperative intra-arterial chemotherapy, surgery, and chemoradiation.

Treatment

Treatment consisted of three parts: (1) neoadjuvant superselective intra-arterial chemotherapy with cisplatin given to the primary, with concomitant systemic sodium thiosulfate for neutralization, followed by (2) surgery and (3) adjuvant chemoradiation with weekly doses of docetaxel. Treatment was initiated with one cycle of preoperative intra-arterial high-dose cisplatin at 150 mg/m² given on an inpatient basis (hospital admission for 4–6 days due to health care system guidelines). If a near to complete partial response was achieved, as determined by clinical examination and CT scan, one or two additional cycles of intra-arterial cisplatin were given 3 weeks apart. (The maximum number of cycles was restricted to three.) On day 1 of each neoadjuvant chemotherapy cycle, patients received hyperhydration and other supportive measures as described elsewhere [22]. Using a transfemoral approach, a 4-french catheter containing a coaxial micro-catheter for superselective visualization of the tumor-feeding vessel by means of fluoroscopy and contrast medium was inserted, and cisplatin (medac GmbH, Wedel, Germany) at a dose of 150 mg/m² (maximum absolute dose, 300 mg) and diluted in 500 ml of 0.9% saline solution was infused at controlled pressure (2 ml/s). For analgesia, 0.1 to 0.3 mg of fentanyl was given intravenously, and in case of perfusion of the maxillary artery with occasional tooth ache, 5 to 15 mg of mepivacain was injected into the perfused artery. 10 s after initiation of the cisplatin infusion, a concomitant intravenous infusion of 9 g/m² of sodium thiosulfate was started and continued for the duration of intra-arterial cisplatin administration. After completion of chemoperfusion, hyperhydration and supportive treatment were resumed and continued until day 2.

Assessments

All patients had pretreatment staging including palpation, ultrasound, computer tomography (CT) and magnetic resonance imaging (MRI) for the diagnosis of the primary and involved neck lymph nodes, and chest X-ray and positron emission tomography (PET) with 2-[F18]-fluoro-2-deoxy-D-glucose for the diagnosis of secondary tumors, neck lymph node involvement, or distant metastases.

Routine laboratory studies were performed on alternate days after the start of neoadjuvant treatment, and toxicity was graded using WHO criteria [27]. 3 weeks after the first cycle, response to therapy was assessed by visual inspection, palpation, and CT scan. A complete response (CR) was defined as complete clinical and radiologic disappearance of the local tumor. A partial response (PR) was a greater than 50% reduction in size of the tumor. Progressive disease (PD) was a greater than 25% increase in size of the local tumor or appearance of new lesions. Tumor responses that did not meet any of the above definitions were designated as stable disease (SD).

Surgery was the second step of this multimodality program (3–4 weeks after neoadjuvant treatment). Since significant downstaging of the tumor was not considered a realistic aim of induction chemotherapy, all resections were intended to include tumor-free margins based on the tumor extension prior to therapy (which was also recorded on photographs). Deep infiltration was assessed by comparison of pretherapeutic and presurgical CTs and intraoperative palpation. Surgical treatment was carried out according to the guidelines of the German-Austrian-Swiss Cooperative Group on tumors of the maxillofacial region (DÖSAK) [5], with two important modifications. First, patients with N0 disease after baseline staging including PET underwent only ipsilateral suprahyoid neck dissection (a selective neck dissection including levels I and II), irrespective of the localization and size of the primary tumor. Second, a radical neck dissection was carried out only in cases of fixed lymph nodes; in all other cases of lymph node involvement at baseline, and independent of the side, a type III modified radical neck dissection was performed. If the histological examination of the dissection material revealed a positive finding despite baseline N0 staging, a lower neck dissection that included levels III to V was performed as soon as possible to eventually result in a modified radical neck dissection. In case of positive surgical margins (invasive microscopic cancer at the resection margins), an additional resection at the respective site(s) was carried out. The classification of neck levels and types of operations followed the proposal of the Committee for Neck Dissection Classification of the American Head and Neck Society [31]. The last treatment step involved weekly irradiation of the primary and lymphatic drainage area and concurrent systemic administration of docetaxel (Aventis Pharma S.A., Antony Cedex, France). Before starting chemoradiation, patients were required to complete any dental procedure including surgery and tooth extraction, and to demonstrate completely healed surgical wounds. Mucositis prophylaxis included frequent rinsing of the mouth with dexpantenol and camomile tea. Using thermal plastic masks for immobilization and 3-D planning (HELAX TMS) according to ICRU 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 microscopic local tumor residues were detected at the surgical margin at primary surgery, an

additional boost of 10 Gy was delivered; in case of infiltration of a surgical margin at the additional resection, a boost of 20 Gy (5×/week, 2.0 Gy/day) 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 (suprahyoid 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. The slightly higher daily dose of boost radiation was justified with the smaller target volume.

Concomitant chemotherapy was given on an inpatient basis. Docetaxel was administered as an intravenous infusion over 60 min on day 2 of each weekly cycle of radiotherapy for a maximum of five cycles. Since the optimal dose was unknown at the beginning of the study, three different dose levels of docetaxel (20, 25, and 30 mg/m²) were considered, depending on tolerability. The first 15 patients were planned to start with 30 mg/m² of docetaxel for three cycles, with the dose being adjusted if accumulating toxicities occurred (de-escalation strategy). To prevent edema and hypersensitivity reactions, the patients received oral dexamethasone 4 mg bid 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. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria v. 2.0. [34].

Endpoints

These were stage-related and overall survival (primary endpoint), relapse history, feasibility and early plus long-term late toxicity of concurrent radiation and chemotherapy with weekly docetaxel (secondary endpoints). Survival by stage, and overall and disease-free survival was calculated using the Kaplan-Meier method [20]. The deadline for survival assessment was August, 2003.

Results

Patient Population

From November 1997 to May 2002, 94 eligible patients (71 male, 23 female) were enrolled in the study. The patient characteristics are shown in Table 1. Median age was 59 years (range, 38–77), and median performance status according to Eastern Cooperative Oncology Group (ECOG) was 0. The most frequently involved tumor sites were the floor of the mouth, tongue, mandibular alveolar process, and oropharynx. Approximately one half of the patients had stage IV disease according to the UICC classification [36]. The distribution of

T and N stages at baseline is shown in Table 2. Ten patients had a history of another malignant disease treated with curative intention more than 5 years prior to entry into this study. The diagnosis included lung cancer (3 patients), prostate cancer (2 patients), SCC of the floor of the mouth, SCC of the palate, SCC of the hypopharynx, SCC of the esophagus, and breast cancer (1 patient each). PET scans were negative at all these sites.

Treatment Administration

The actually delivered treatment modalities and duration of treatments are outlined in Table 3. Intra-arterial chemotherapy with cisplatin resulted in a clinical overall response rate (CR + PR) of 56%, with 14 CR, 39 PR, 40 SD, and 1 PD. Local pathologic staging demonstrated a pCR rate of 10% (9 patients); the remaining patients had the following T stages: pT1 (25 patients), pT2 (28 patients), pT3 (3 patients), and pT4

(29 patients), indicating a shift in the distribution of primary tumor size to smaller tumors. Surgery was locally radical in all patients, with a high rate of selective neck dissection (50%). 15 patients (16%) had narrow or positive surgical margins that required additional local resection.

All patients routinely received a percutaneous endoscopic gastrostomy (PEG) tube before the starting of radiation to ensure sufficient nutrition during therapy.

The first dose level of docetaxel given with concomitant radiation was 30 mg/m². However, this dose had to be reduced after the first 13 consecutive patients because 2 patients developed grade IV mucositis, and one patient each had grade 1 thrombocytopenia, and hyperuricemia with gout. One patient suffered from a fatal renal failure (yielding a 1% mortality risk in this study). The following patients received docetaxel at doses of 25 mg/m² (51 patients) or 20 mg/m² (30 patients). These doses were better and equally well tolerated; thus, the maximum tolerated dose (MTD) of docetaxel with concomitant radiation was defined as 25 mg/m² in the adjuvant setting. The median number of cycles of docetaxel in the total population was 5 (range, 1–5), with 54 patients (57%) receiving all scheduled cycles. The mean number of cycles

Table 1. Patient characteristics.

Tabelle 1. Patientencharakteristika.

Characteristic	n (%)
No. patients	94
Gender	
Male	71 (76)
Female	23 (24)
Median age, years (range)	56 (38–77)
ECOG performance status	
0	70 (74)
1	21 (22)
2	3 (3)
Primary tumor site	
Floor of the mouth	33 (35)
Tongue	19 (20)
Mandibular alveolar process	15 (16)
Oral cheek mucosa	6 (6)
Retromolar trigone	6 (6)
Maxilla	4 (4)
Oropharynx	11 (12)
Stage	
I	13 (14)
II	14 (15)
III	17 (18)
IV	50 (53)

Table 2. Distribution of T and N classifications at baseline.

Tabelle 2. Prätherapeutische Verteilung der T- und N-Klassifikationen.

	N0	N1	N2a	N2b	N2c	N3	Total
T1	13	2	0	0	0	0	15
T2	14	6	0	3	0	0	23
T3	3	6	0	1	1	0	11
T4	16	12	1	12	3	1	45
Total	46	26	1	16	4	1	94

Table 3. Delivered treatment modalities. MRND: modified radical neck dissection; ND: neck dissection.

Tabelle 3. Verabreichte Behandlungsmodalitäten. MRND: modifiziert radikale Neck-Dissektion; ND: Neck-Dissektion.

Treatment/Duration/Specification	No. Patients (%)
Intra-arterial chemotherapy	94 (100)
1 cycle	85 (90)
2 cycles	7 (7)
3 cycles	2 (3)
Local operation	94 (100)
With mandibular continuity resection	22 (23)
With soft tissue and/or rim resections	72 (77)
Neck dissection	92 (98)
Bilateral MRND	9 (10)
Ipsilateral MRND	21 (22)
Ipsilateral MRND + contralateral selective ND (I-II)	17 (18)
Bilateral selective ND (I-II)	21 (22)
Ipsilateral selective ND (I-II)	10 (11)
Unilateral sentinel node biopsy	8 (9)
Bilateral sentinel node biopsy	6 (6)
No neck dissection	2 (2)
Radiation	
51.3 Gy to tumor + lymph nodes	94 (100)
+ Boost 10 Gy	10 (11)
+ Boost 20 Gy	5 (5)
Concomitant chemotherapy	94 (100)
Docetaxel 30 mg/m ² (3 scheduled cycles)	13 (14)
Docetaxel 25 mg/m ² (5 scheduled cycles)	51 (54)
Docetaxel 20 mg/m ² (5 scheduled cycles)	30 (32)
All scheduled cycles administered	54 (57)
Mean no. (range) of cycles in patients with docetaxel discontinuation	2.6 (1–4)
Median no. of cycles among all patients	5

Table 4. Acute and chronic toxicities following chemoradiation with docetaxel.**Tabelle 4.** Akute und chronische Toxizität nach Radiochemotherapie mit Docetaxel.

% of Patients	Mucositis Grade				Dermatitis Grade				Xerostomia Grade				Edema Grade			
	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
During chemoradiation	11	34	46	9	37	58	5	0	21	64	15	0	3	0	0	0
3–6 months posttreatment	25	25	0	0	63	4	0	0	63	4	0	0	21	25	0	0
6–12 months posttreatment	26	5	0	0	21	5	0	0	74	0	0	0	21	5	0	0
2–3 years posttreatment	10	0	0	0	0	0	0	0	68	10	0	0	0	15	0	0
3–5 years posttreatment	5	0	0	0	0	0	0	0	63	5	0	0	10	5	0	0

among those with early discontinuation of docetaxel was 2.6 (range, 1–4).

Acute and Late Toxicities

Acute toxicities of chemoradiation at the 25 and 20 mg/m² dose levels that prompted withdrawal of docetaxel included grade III or IV mucositis (22 patients), hypersensitivity reactions with flush syndrome (2 patients), grade IV dermatitis (2 patients), fluid retention (facial edema) (1 patient), and grade III transaminase elevation (1 patient). More common acute and late toxicities of chemoradiation occurring in all patients are summarized in Table 4. Toxicity generally decreased during the follow-up which extended over a period of more than 3 years. At 6 months, grade III or IV mucositis was no longer seen, and half of the patients were free of signs and symptoms of mucositis. Dermatitis and xerostomia also decreased gradually during follow-up, although mild to moderate xerostomia persisted for up to 3 years or longer in the majority of patients. The incidence of mild to moderate facial edema increased sharply at 3–6 months posttherapy and persisted throughout follow-up in some patients. The incidence of hypersensitivity reactions was remarkably low (see above). In 6 of 22 patients, the metal plate bridging the mandibular defect had to be removed because of extreme shrinking of the skin with consecutive exposure of the implant. Surgical scars remained stable after chemoradiation, and therefore no significant mandibular deviation occurred. Three patients had secondary mandibular reconstruction with microsurgical fibula transfer that was not associated with any complications. In two patients, osteoradionecrosis of the mandible required surgical measures.

Treatment Outcome

To date, 18 patients have developed recurrent disease (local relapse in 9 patients, lymph node metastases in 3 patients, distant metastases in 5 patients, and both locoregional recurrence and distant metastasis in 1 patient). Two initially suffered from clinical stage III disease, 16 had clinical stage IV disease. Three local recurrences were eligible for salvage surgery, and the locoregional relapses were treated with neck dissection. The patients with distant metastases received palliative che-

motherapy with low-dose methotrexate. Seven additional patients developed metachronous tumors at other sites (lung, 4 patients; brain, 2 patients; oral cavity, 1 patient). 23 patients have died, but 6 deaths were not related to the malignant disease (3 heart failures, 1 trauma, 1 stroke, 1 treatment-related renal failure).

All patients were included in the survival analysis. At a median follow-up of 4 years (range, 18–77 months), the actuarial 5-year overall survival rate was 80%, and disease-free survival, defined as survival without local or locoregional relapse or distant metastatic disease, was 73% (Figures 1 and 2). For the 51 patients treated with 25 mg/m² of docetaxel, the respective survival rates were 82% and 75%. Of note, survival was far over 80% among patients with tumors of small to intermediate size (stages I–III; Figures 3 and 4). Among patients with advanced disease (stage IV), survival was 59% for all patients (Figure 4) and 56% for those receiving 25 mg/m² of docetaxel.

Discussion

In recent years, significant interdisciplinary efforts have been made to improve treatment results in patients with oral and oropharyngeal cancer. One of the major targets of interest has been the combination of chemotherapy and radiation. Published data demonstrated that in the non-surgical setting, the combination of high-dose radiotherapy (up to 70 Gy) and chemotherapy using conventional agents like cisplatin and fluorouracil resulted in significantly improved survival rates compared with radiation alone [1, 6, 7]. However, the 5-year survival rates never exceeded 50%. Mucositis was the main acute side effect requiring naso-gastral tubes for more than 6 weeks in the majority of patients.

Therefore, new antineoplastic agents have been evaluated, and the use of the taxanes for the treatment of patients with head and neck cancer is under intensive investigation since several years. Paclitaxel seems to be more effective as long-term infusion [15, 38] whereas docetaxel offers the possibility of a short 1-hour infusion. In phase II studies of chemotherapy for recurrent and incurable head and neck cancer, overall response rates of up to 42% were achieved with 100 mg/m² of docetaxel given every 3 weeks [10, 12]. Most side

effects were acute and of short duration, including leukopenia (up to 61%), alopecia (up to 90%), hypersensitivity reactions (up to 23%), skin toxicities (54%), and peripheral edema (31%). These toxicities required a reduction in the dose of docetaxel in up to 40% of the patients. The recommended dose of weekly docetaxel chemotherapy alone was shown to be 36 mg/m² [13]. Weekly schedules are well suited for concurrent chemoradiation but the docetaxel dose must clearly be lowered. In combination with radiation therapy, the maximum tolerated dose of docetaxel has not yet been defined. In 42 patients with bladder cancer who received postoperative chemoradiation (68–74 Gy in daily fractions of 2 Gy with weekly doses of 30 mg/m² of cisplatin), the addition of docetaxel at weekly doses of 40 mg/m² was not tolerated, and the dose had to be reduced to 20 mg/m² [43]. This latter dose seemed to be well tolerated in combination with 60 Gy for the treatment of non-small-cell lung cancer and esophageal cancer [26]. In several studies of advanced inoperable head and neck cancer, the administration of weekly doses of 15–30 mg/m² of docetaxel was found to be feasible with concomitant radiation at doses of up to 70 Gy [16, 21, 40]. Docetaxel was also successfully included in sequential multiagent chemoradiation protocols [9, 18] or administered as single agent in the palliative setting [33].

In the present study, patients with oral or oropharyngeal cancer were treated with intra-arterial cisplatin followed by surgery and postoperative chemoradiation with docetaxel. Local relapses represent the crucial problem in the treatment of this disease. Therefore we considered a combination of several locally active treatment modalities a reasonable and promising approach. Published data suggest that intra-arterial high-dose chemotherapy is associated with a very low incidence of acute systemic side effects [22–24]; this is particularly important for the treatment of patients with a high comorbidity. Our results confirm that high-dose intra-arterial cisplatin is feasible, well tolerated and highly effective. Nearly all patients received the scheduled treatment, and the local overall response rate of 56% assessed after one single cycle is impressive. However, the emphasis of our study lay on the novel use of docetaxel in the adjuvant setting. Weekly doses of 20 or 25 mg/m² could be

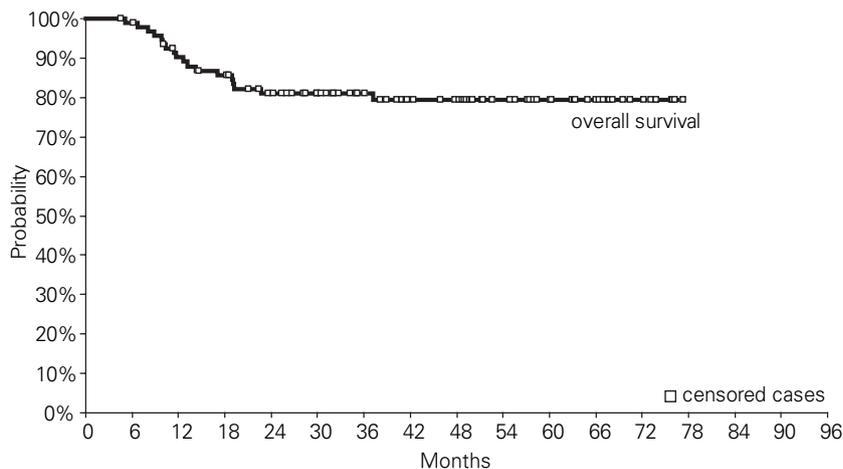


Figure 1. Overall survival (94 patients).

Abbildung 1. Gesamtüberleben (94 Patienten).

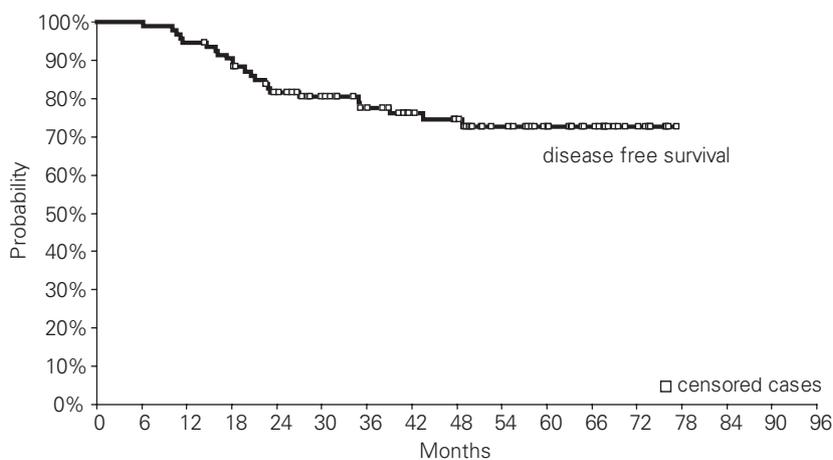


Figure 2. Disease-free survival (94 patients).

Abbildung 2. Krankheitsfreies Überleben (94 Patienten).

readily combined with a radiation dose of 51.3 Gy. Mucositis was the main acute toxicity of chemoradiation, reaching grade III and IV in 55% of the patients. Therefore, supportive therapy as mentioned above was mandatory, as was the use of PEG tubes from week 4 or 5 of chemoradiation. At the same time, discontinuation of chemotherapy became advisable in some patients. To date, there does not seem to exist a reliable means to prevent chemotherapy-induced mucositis [32]. Remarkable was the low incidence of systemic adverse effects such as hematologic toxicity or hypersensitivity reactions. In a recent report of a regimen consisting of weekly cycles of docetaxel with concurrent radiation (68–72 Gy) following induction therapy for locally advanced head and neck cancer, the 25 mg/m² dose level of docetaxel also proved to be tolerable even though all patients developed grade III mucositis and pain [40].

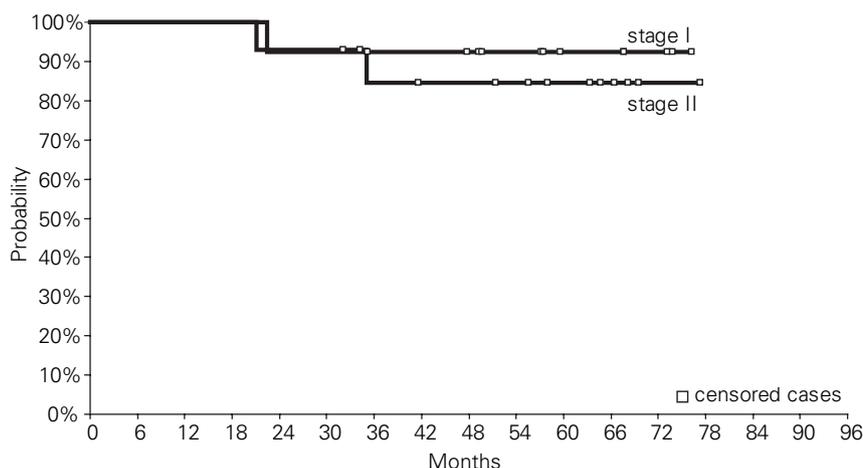


Figure 3. Survival by stages I (13 patients) and II (14 patients).

Abbildung 3. Überleben der Patienten in den Stadien I (n = 13) und II (n = 14).

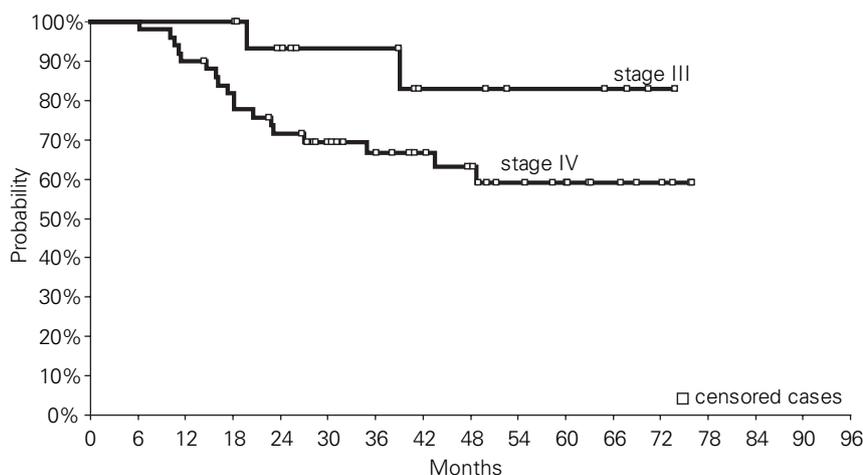


Figure 4. Survival by stages III (17 patients) and IV (50 patients).

Abbildung 4. Überleben der Patienten in den Stadien III (n = 17) und IV (n = 50).

Thus far, few studies have investigated postoperative concurrent chemoradiation in patients with head and neck cancer. A major randomized study was conducted by Bachaud et al. [4] in patients with stage III–IV disease who had positive lymph nodes with perinodal tumor spread. Postoperative radiotherapy alone was compared in this study with concurrent radiation and chemotherapy using 7–9 weekly cycles of intravenous cisplatin 50 mg. 5-year overall survival was significantly improved with chemoradiation (36% vs. 13%). That survival advantage appeared to be related to a reduced local recurrence rate. Grade III or IV toxicities occurred in 41% of patients in the chemoradiation arm. 18% of the patients received less than two thirds of the scheduled chemotherapy due to significant nausea and vomiting [3]. In the RTOG-trial 88-24 [2], 51 patients received radiotherapy and concurrent

cisplatin 100 mg/m² on days 1, 23, and 43. Actuarial 3-year-survival was 48%, and the incidence of local recurrence seemed to be reduced compared with a historical control group treated with postoperative irradiation alone. Acute toxicity was observed in 20% of patients. Radiation had to be discontinued in 10% of the patients, and 39% received less than three cycles of chemotherapy.

Compared with these studies, outcome was superior in our trial of postoperative radiotherapy and concurrent docetaxel, with a 5-year-survival of 83% in stage III and 59% in stage IV patients. These results appear particularly noteworthy in view of the lack of stringent patient selection (the only inclusion criterion for our study was patient operability). The survival of patients with early stage disease (85–92%) has to be judged as an improvement in the light of the data of the German-Austrian-Swiss tumor registry where these patients have a survival below 70% [17]. It is known that most clinics contributing to the registry treated these stages with surgery alone. The implementation of the German guidelines for standard treatment which recommend surgery and postoperative radiotherapy for tumor stages I and II [11] has still to be regarded as a desideratum even if the adjuvant chemoradiation proposed in the present study may be estimated as overtreatment for these stages.

Moreover, compliance to therapy was acceptable when compared to published study data, and the incidence of acute toxicities following chemoradiation with docetaxel appear similar to those observed with concurrent cisplatin. Therefore it appears that docetaxel has the potential to replace platinum agents in combined chemoradiation protocols. However, we cannot exclude an increased overall toxicity burden as a result of our multimodality treatment approach that added neoadjuvant chemotherapy to surgery and adjuvant chemoradiation. Therefore, intensive efforts must continue to improve the prevention of acute as well as late sequelae of chemoradiation.

At present, a final conclusion as to the efficacy of our treatment program with regard to local recurrence rate and long-term survival is not yet possible because of the still limited follow-up. Future studies will have to demonstrate if this treatment schedule is justified, especially in patients with lo-

cally advanced oral or oropharyngeal cancer, as compared to definitive chemoradiotherapy with concurrent docetaxel as reported by Calais et al. [8]. In that study which combined conventional radiotherapy at 70 Gy with weekly docetaxel 20 mg/m², the actuarial 3-year survival rate was 47% and the local control rate 64% at a median follow-up of 37 months. Only 41% out of 61 patients required a feeding tube although grade III and IV mucositis occurred in 84% of the patients. Outcome, however, was far below the one reported on the present multimodality approach. Another strategy to improve treatment outcome in head and neck cancer may be the use of hyperfractionated radiation. However, the usefulness of this approach based on published data remains controversial [19, 37]. Very aggressive definitive simultaneous radiochemotherapy with accelerated hyperfractionated radiotherapy may have a high rate of therapy-related deaths [25]. Moreover, a critical appraisal of the late effects of any kind of multimodality therapy is essential and must be balanced against the potential benefits of treatment. Instead of a comparison of side effects of neoadjuvant radiochemotherapy and postoperative radiotherapy [45], which might not be appropriate, the present report offers the possibility to judge postoperative radiochemotherapy more adequately. How important the issue of life quality may be, however, long-term survival must remain the main goal of cancer treatment.

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