Feasibility, Toxicity, and Efficacy of Short Induction Chemotherapy of Docetaxel Plus Cisplatin or Carboplatin (TP) Followed by Concurrent Chemoradiotherapy for Organ Preservation in Advanced Cancer of the Hypopharynx, Larynx, and Base of Tongue

Early Results

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Purpose: Concurrent chemoradiotherapy (CRT) is standard treatment for advanced head and neck cancer. Whether short induction chemotherapy (ICT) provides additional benefit or, in particular, predictive benefit for the response to chemoradiotherapy is an open question. The present study aimed to assess the feasibility, toxicity, and efficacy of induction with docetaxel and platinum salt (TP) and subsequent CRT.

Patients and Methods: A total of 25 patients with functionally inoperable cancer of the base of the tongue, hypopharynx, or larynx received 1 cycle of docetaxel (75 mg/m², day 1) combined with either cisplatin (30 mg/m², days 1–3; n = 23) or carboplatin (AUC 1.5 days 1–3; n = 2). Responders (n = 22, >30% tumor reduction, graded by endoscopy) and 1 non-responder received CRT (target dose: 69–72 Gy) with cisplatin/paclitaxel, carboplatin/paclitaxel, or cisplatin/docetaxel.

Results: All patients completed ICT with acceptable toxicity (leukocytopenia grade 4: 8%). The remission rate of the primary tumor was 88% (22/25 patients). There was no need to delay CRT due to toxicity in any case. Each patient received the full radiation dose. Of the patients, 56% received >80% of the chemotherapy. The acute toxicity of CRT was moderate, no grade 4 toxicities occurred, while grade 3 toxicities included the following: infection (39%), dermatitis (13%), leukocytopenia (30%), and thrombocytopenia (4%). The local control rate was 84.6% ± 8.5% and the survival rate was 89.6% ± 7.2% at 12 months. Organ preservation was possible in 22/23 (95%) cases.

Conclusion: Short induction with a TP regimen and subsequent CRT with a taxan is feasible and associated with an encouraging local control rate.

Key Words: Laryngeal cancer · Hypopharyngeal cancer · Induction chemotherapy · Chemoradiation

Strahlenther Onkol 2010
DOI 10.1007/s00066-010-2178-2

Durchführbarkeit, Toxizität und Effektivität der Kurzinduktionschemotherapie mit Docetaxel und Cisplatin oder Carboplatin (TP) vor Radiochemotherapie (RCT) zum Organerhalt bei Patienten mit Hypopharynx-, Larynx- und Zungengrundkarzinomen – Erste Ergebnisse

Ziel: Die simultane Radiochemotherapie (CRT) ist Standard bei fortgeschrittenen Kopf-Hals-Tumoren. Offen ist der Stellenwert einer Kurzzeitinduktionschemotherapie (ICT), insbesondere deren prädiktive Bedeutung für das Ansprechen der Radiochemotherapie. In der Studie werden Durchführbarkeit, Toxizität und Effektivität einer Induktionschemotherapie mit Docetaxel und einem Platinsalz einschließlich der folgenden RCT berichtet.

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Received: May 18, 2010; accepted: September 29, 2010
Published online: December 22, 2010

Patienten und Methode: 25 Patienten mit einem nicht funktionserhaltend operablen Zungengrund-, Hypopharynx- und Larynxkarzinom erhielten einen Zyklus Docetaxel (75 mg/m², d1) und Cisplatin (30 mg/m² d-1–3) (n = 23) oder Carboplatin (AUC 1,5 d1-3) (n = 2). Responder (n = 22, mehr als 30% Rückbildung endoskopisch) und ein Non-Responder erhielten nachfolgend eine RCT (Zieldosis: 69–72 Gy) mit Cisplatin/Paclitaxel rsp. Carboplatin/Paclitaxel oder Cisplatin/Docetaxel.
Ergebnisse: Die Induktionstherapie konnte bei allen Patienten mit akzeptabler Toxizität (Leukozytopenie Grad 4: 8%) durchgeführt werden. Die Remissionsrate des Primärtumors betrug 88% (22/25 Pat). Die Radiochemotherapie wurde in keinem Fall toxizitätsbedingt verzögert. Die Radiotherapiedosis wurde vollständig gegeben. 56% der Patienten erhielten >80% der geplanten Chemotherapie. Die Akuttoxizität der RCT war moderat, keine Grad-4-Toxizität; Grad-3-Toxizitäten: Infektion (39%), Dermatitis (13%), Leukozytopenie (30%), Thrombozytopenie (4%). Nach 12 Monaten lag die Lokalkontrolle bei 84,6% ± 8,5%, das Gesamtüberleben 89,6% ± 7,2%. Die Organerhaltquote lag bei 95% (22/23).
Schlussfolgerung: Die Kurzinduktion mit TP und die nachfolgende CRT mit einem Taxan sind durchführbar und führten zu einer ermutigenden Tumorkontrolle.

Schlüsselwörter: Larynxkarzinom · Hypopharynxkarzinom · Induktionschemotherapie · Radiochemotherapie

Introduction

Concurrent chemoradiotherapy (CRT) is the standard treatment for laryngeal and hypopharyngeal cancer, the surgical resection of which would endanger preservation of the patient's ability to swallow or speak. Compared to primary surgery, the use of CRT for organ preservation does not result in a survival disadvantage [6, 7, 12, 13, 21].

However, there are some arguments against primary CRT. In essence, if complete remission is not achieved, surgical salvage treatment could be difficult and the functional outcome of CRT may be uncertain. Significant room for improvement, therefore, lies in the enhancement of the efficacy of both radiotherapy and chemotherapy and the identification of patients who will not respond to CRT.

Induction regimens focus on the areas of patient selection and treatment escalation, whereby decisions regarding the combination partner, the number of treatment cycles, and the later selection criteria are based on historical evidence. Integrating taxanes into the induction and CRT without impairing the feasibility of CRT is in one area of interest and the determination of early markers of prediction of the later response is crucial.

Based on this rationale, we developed a protocol using taxotere in combination with a platinum derivative for single cycle induction chemotherapy (ICT) prior to a taxane-containing CRT. The results of the feasibility and toxicity assessments and early data on the efficacy with a focus on the proportion of prevented surgical procedures are presented here.

Patients and Methods

Inclusion Criteria

From March 2008 to September 2009, 25 patients with squamous cell carcinomas of the larynx, pharynx, or base of the tongue expected to result in functional impairment if treated surgically were recruited. Colleagues from the Otolaryngology Department of the University of Erlangen-Nuremberg participated in the selection process. Further eligibility requirements were ECOG 0–2, a maximum age of 78 years, and written informed consent after individual counseling informing them of the nature and scope of the procedure and the possible treatment alternatives.

Diagnostics

For assessment of the extent of spread, whole-body PET/CT, ultrasound of the neck, and contrast-enhanced computed tomography (CT) were routinely performed prior to the start of treatment. The response to treatment was evaluated by panendoscopy, CT and PET/CT 3 weeks after ICT and 6 weeks after CRT.

The chief criteria for recommendation of CRT following ICT were significant reduction of dimension (>30%) of the primary tumor as determined by endoscopy, significant reduction of glucose uptake (≥20%) in the primary tumor as determined by PET/CT, and the absence of tumor progression as determined by CT. Eligible patients received the recommendation to continue on to CRT. If incomplete tumor regression was diagnosed after CRT, salvage resection of the primary tumor was performed 3 months posttreatment. Neck dissection was performed in cases where lymph node involvement was still suspected.

Treatment

Induction Chemotherapy

Patients received 1 cycle of ICT with the aforementioned TP regimen. It was possible to replace cisplatin with carboplatin in cases where creatinine clearance was inadequate or if hydration did not appear feasible. The dosage schedule is depicted in Figure 1. CRT was scheduled to begin 4 weeks to no more than 5 weeks after induction.

Chemoradiotherapy

CRT was performed using a combination of cisplatin/paclitaxel (n = 16), carboplatin/paclitaxel (n = 5), or cisplatin/docetaxel (n = 2). See Figure 1 for details. A switch to carboplatin was permissible under the aforementioned conditions. Chemotherapy was not performed in patients with leukocytopenia (<3 Gpt/l), thrombocytopenia (<100 Gpt/l), or dermatitis (grade 3 or higher). Individual doses of paclitaxel or docetaxel could be postponed for no more than 2 days; doses of cisplatin

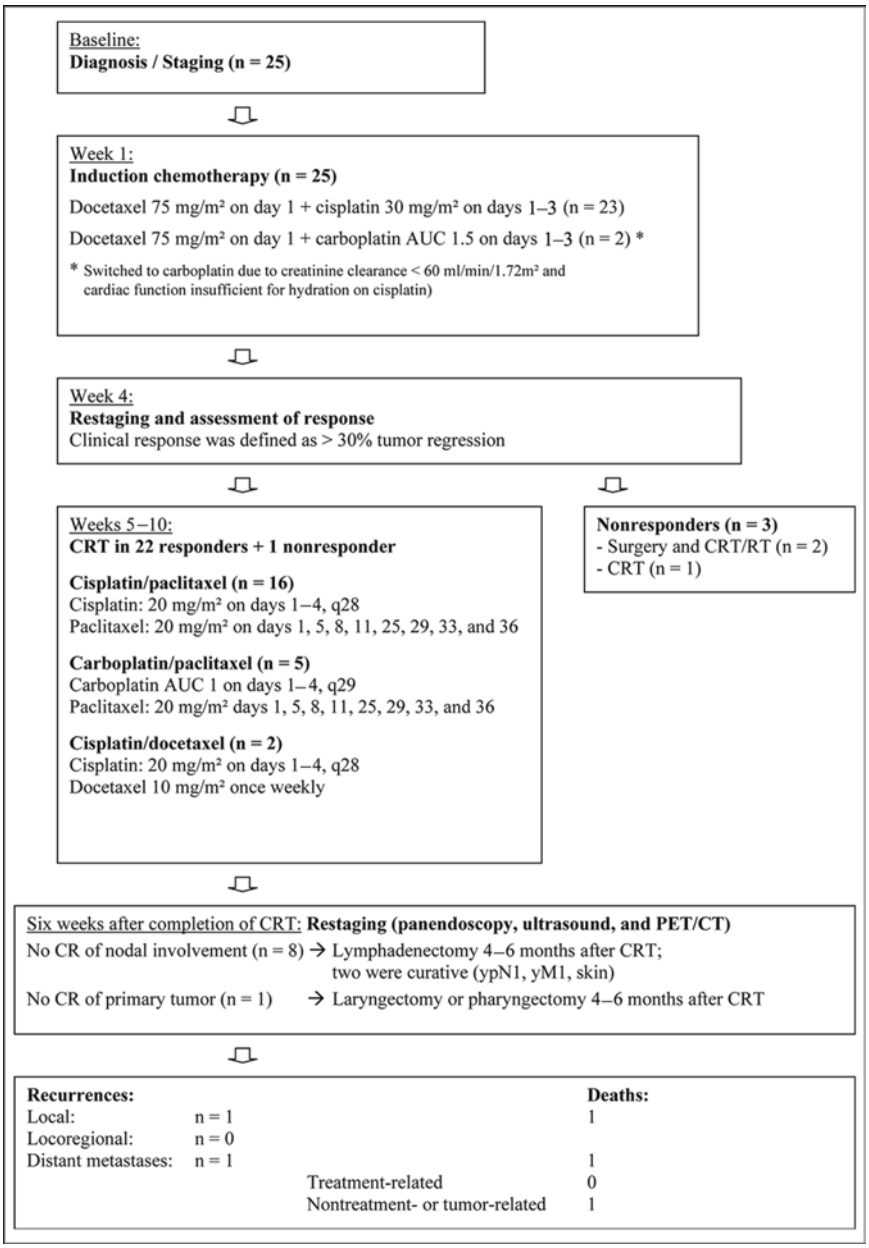

Figure 1. Protocol using taxotere in combination with a platinum derivative for single cycle ICT prior to a taxane containing CRT.

Abbildung 1. Therapieprotokoll der Induktionschemotherapie mit Docetaxel und einem Platinderivat vor einer taxanhaltigen RCT.

or carboplatin could be postponed for no more than 1 week in the second cycle or cancelled if there was insufficient restoration of myelopoesis.

Radiotherapy was administered using a 6 MV linear accelerator according to three-dimensional (3D) planning. The goal was to deliver a dose of 72 Gy to the primary tumor region and the affected lymph nodes. Lymph nodes with a high risk of locoregional recurrence received a dose of 58.0 Gy, and those with a low risk of locoregional recurrence a dose of 49.6 Gy. The dose was conventionally fractionated in the first 3 weeks (5×2 Gy/week), then hyperfractionated (2×1.4 Gy/day). For target volume definition, the pretreatment CT and PET/CT were used.

Criteria of Analysis

Acute adverse events occurring from the induction phase until the 6-week follow-up after CRT were classified according to the Common Terminology Criteria of Adverse Events (Version 3). Functional and cosmetic outcomes were assessed according to the LENT-SOMA criteria at the latest follow-up date and no sooner than 6 weeks after completion of treatment. The available baseline data were not sufficient for comparison.

The efficacy was evaluated based on the primary characteristics at baseline and on the results of panendoscopy. Biopsy results were also used in cases where complete remission was questionable after treatment. The response of lymph node metastases to the ICT and CRT was disregarded because of the possibility of subsequent neck dissection.

Statistical Analysis

The primary efficacy variable was a complete remission rate of more than 85% (primary tumor) 6 weeks after CRT, as confirmed by panendoscopy. Progression-free survival and survival were calculated from the start of the protocol and estimated by Kaplan–Meier analysis. By 31 March 2010, all patients had been followed up for at least 6 months.

Results

Patients

The large majority of patients in the study population had stage III or IVa (88%) cancer of the hypopharynx (40%) or larynx (40%). The percentages of patients in the individual tumor stages are listed in Table 1.

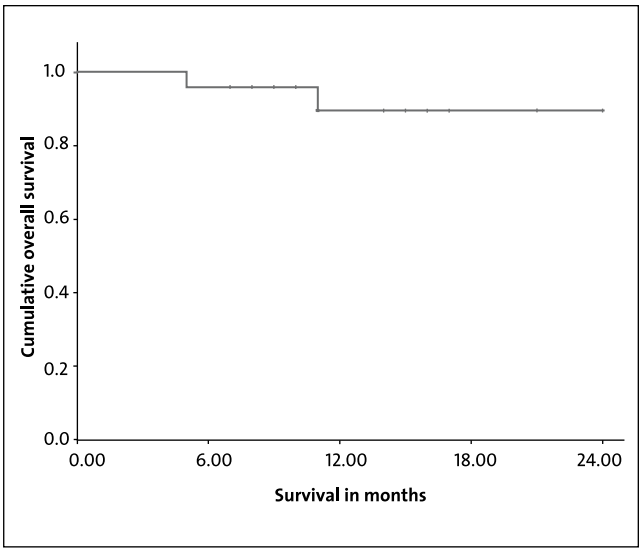

Figure 2. Kaplan–Meier estimates of cumulative overall survival for all 25 patients.

Abbildung 2. Gesamtüberleben aller 25 Patienten nach Kaplan–Meier.

Table 1. Patient characteristics.

Tabelle 1. Patientencharakteristik.

	Number of patients (n = 25)	Percentage (%)
Sex		
Male	23	92
Female	2	8
Primary site		
Mesopharynx	5	20
Hypopharynx	10	40
Larynx	10	40
T stage		
T2	8	32
T3	10	40
T4	7	28
N stage		
N0	6	24
N1	0	0
N2a	1	4
N2b	9	36
N2c	8	32
N3	1	4
UICC stage (7th edition)		
II	3	12
III	6	24
IVa	15	60
IVb	1	4

Feasibility of Treatment

Induction Chemotherapy

ICT was performed within 3 days in all cases. Out of 25 patients, 2 had received carboplatin (Figure 1). CRT was initiated 4–5 weeks after induction in 23/25 patients, and 6–7 weeks in 2 patients due to organizational reasons.

Chemoradiotherapy

After ICT, 23 patients received CRT and 2 underwent surgery (resection of base of tongue or larynx). All patients received the target radiation dose of 69–72 Gy. Because of tumor bleeding, one patient received a dose of 63 Gy after starting with a single dose of 3 Gy. The estimated biologically effective dose was greater than 69 Gy.

CRT was performed using paclitaxel plus cisplatin in 16 cases, paclitaxel plus carboplatin in 5 cases, and cisplatin plus docetaxel in 2 cases. The latter treatment regimen was abandoned due to severe skin toxicity at docetaxel dose level 1 (10 mg/m^2/week).

In the end, 56% of the patients received at least 80% of the planned dose, i.e., a minimum of either cisplatin (140 mg/m^2) or carboplatin (AUC 7) was combined with paclitaxel (140 mg/m^2). Chemotherapy dose escalation was not pursued in 6 of the first 10 patients due to a lack of feasibility, at least, of the last paclitaxel infusion. The 2 patients treated with docetaxel received 30 mg/m^2 and 40 mg/m^2 together with cisplatin 140 mg/m^2 and 100 mg/m^2.

Toxicity

No serious adverse events occurred during ICT. Notable events were grade 4 leukocytopenia (8%), which proceeded without complications but prevented further dose escalation, and reduced renal clearance (grade 1 in 4 cases and grade 2 in 1 case).

Increased susceptibility to infection was a frequent side effect of CRT. Antibiotics were required in 16 patients (69%). All higher grade hematological toxicities caused no complications. Grade 3 dermatitis developed in 3 patients, 2 of whom received docetaxel during radiotherapy. Relevant toxicities are listed in Table 2.

Response to ICT and Treatment Decision-Making

In 7/25 (28%) patients, a single induction cycle induced clinically complete tumor regression evaluated by endoscopy, which was histologically confirmed in 5 cases (20%). No biopsy was performed in 2 patients. Partial tumor regression occurred in 15/25 patients (60%). No significant response could be detected by endoscopy in 3 patients (12%). Tumor progression did not occur.

Surgery was performed in 2 of the patients showing no significant response to ICT. A total of 23 patients decided to continue on to CRT, including 1 patient with no significant response to ICT.

Table 2. Acute toxicity of induction chemotherapy and chemoradiotherapy.

Tabelle 2. Akuttoxizität der Induktionstherapie und der Radiochemotherapie.

Toxicity	Grade 2 (absolute)	Grade 2 (relative)	Grade 3 (absolute)	Grade 3 (relative)	Grade 4 (absolute)	Grade 4 (relative)
Induction chemotherapy (n = 25)						
Hematologic adverse events						
Anemia	2	8%	1	4%	0	0
Transfusion	3			12%		
Leukocytopenia	5	20%	3	12%	2	8%
Febrile neutropenia						
GOCSF use	0					
Thrombocytopenia	0	0	0	0	0	0
Nonhematologic adverse events						
Infection	1	4%	0	0	0	0
Elevated creatinine	1	4%	0	0	0	0
Bleeding	0	0	0	0	1 (required tracheotomy)	4%
Chemoradiotherapy (n = 23)						
Hematologic adverse events						
Anemia	10	43%	1	4%	0	0
Transfusions	5			21%		
Leukocytopenia	8	35%	7	30%	0	0
Febrile neutropenia	0					
Thrombocytopenia	2	9%	1	4%	0	0
Nonhematologic adverse events						
Infection	7	30%	9	39%	0	0
Elevated creatinine	2	9%	0	0	0	0
Bleeding	0	0	0	0	0	0
Dermatitis	5	22%	3 (2 x CRT with docetaxel)	13%		
Oral mucositis	18	78%	0	0	0	0

Response to CRT

After completion of CRT, 21 of the 23 nonsurgically treated patients had an endoluminal diagnosis of complete tumor regression, which was confirmed by biopsy in 18 cases. One patient refused the final panendoscopy examination but did not exhibit any evidence of residual tumor during the examination by the resident otolaryngology specialist. The tumor persisted in the primary location in 1 patient. With a questionable resection status after laryngectomy, he underwent brachytherapy and is free of tumor up to date.

The complete remission rate for the primary tumor assessed by endoscopy was 22/23 patients (95%) for all receiving CRT and 88% in all 25 patients. The percentage of patients with surgery after ICR or CRT with curative intent was 12% (3/25).

At baseline, 19 of 25 patients had lymph node involvement. CRT was performed in 17 of these patients, 6 of whom still had sonographically abnormal lymph nodes after CRT. One of the 6 also had a skin metastasis. Neck dissection confirmed residual lymph node involvement in 2 of the patients and in 1 skin metastasis. Complete remission following CRT was achieved in 17 (89%) of the 19 patients with initial lymph node involvement.

Disease Control and Survival

The median follow-up duration was 11 months (range, 6–24 months). Of the 22 patients who achieved complete remission following CRT, 1 developed local recurrence and another distant. All patients were without evidence of lymph node recurrence. During follow-up, 3 patients had died: 2 due to disease recurrence and 1 due to nontumor-related causes. Overall, the survival rate was 89.6% ± 7.2% and the local control rate 84.6% ± 8.5% at 12 months. Among the 23 patients who received ICR and CRT, the local control rate was 83.3% ± 9.2% and the survival rate 88.8% ± 7.7% at 12 months.

Table 3. Cosmetic and functional outcomes after ≥6 weeks of follow-up after completion of overall treatment.

Tabelle 3. Kosmesis und Toxizität nach einer Nachbeobachtungszeit von mehr als 6 Wochen nach dem Therapieende.

Functional and cosmetic outcomes (n = 21)	Cases	Percentage (%)
ECOG		
0	8	38
1	13	62
Tracheostomy after treatment	4	19
Before treatment (tumor-related)	1	–
During treatment (bleeding)	1	–
After treatment (toxicity-related)	1	–
After treatment (recurrence-related)	1	–
Voice change (not related to tracheostomy)		
None	8	38
Mild to moderate intermittent hoarseness	9	43
Nutrition		
Complete return to oral nutrition	11	52
Feeding tube used for substitution, patient able to swallow liquids	8	38
Completely tube-dependent	2	10
Pain		
None	19	90
Mild pain with no functional impairment	2	10
Mucositis		
None	19	90
Erythema	1	5
Ulceration (patchy)	1 (oral)	5
Ulceration (confluent)	1	5
Salivary gland changes		
None	3	14
Slight enlargement of the salivary glands	10	48
Saliva thick, viscous and sticky; noticeable taste alteration	7	33
Severe secretory symptoms affecting daily activities	1	5
Lymphedema		
None	8	38
Localized without functional impairment	9	43
Localized with functional impairment	2	8
Generalized head and neck edema	2	8
Hyperpigmentation		
None	5	24
Mild and local	15	71
Severe	1	5
Telangiectasia		
None	19	90
Few	2	10
Fibrosis		
None	10	47
"Sponginess" of grip	6	29
Stiffness and tension	5	24
Vision		
No change	20	95
Symptomatic/no impairment	1	5
Hearing		
No change	20	95
Hearing loss (no hearing aid required)	1	5

Functional Outcomes

Data from 21 of the 23 patients who received ICT plus CRT were available. The results are presented in Table 3. All patients rated their general health as good to very good. Four patients had a tracheostomy. Tracheostomy had been performed before treatment in 2 cases, and after treatment (due to laryngeal edema and bleeding, respectively) in the other 2. All of the other patients reported having either no speech problems or moderate hoarseness causing no significant subjective impairment. The rehabilitation outcomes for swallowing function were not as good: 11 patients (52%) were completely feeding tube-free and resumed a normal diet with no weight loss, while 8 were partially and 2 were completely tube-dependent.

Discussion

This study demonstrates that ICT and CRT with a taxane and a platinum derivative are feasible and well tolerated. A single induction cycle induced the required response in the vast majority and did not affect the feasibility of local therapy. ICT and CRT induced complete remission in more than 80% of the patients with a low rate of secondary resections so far.

The actual proposed CRT was designed to enable the integration of taxanes, which have proved to be very effective in combination with cisplatin with or without 5-fluorouracil and with radiotherapy [1, 3, 10]. In 2003, Kuhnt et al. [11] proposed a concurrent chemoradiation in which cisplatin (20 mg/m²/day) was administered on days 1–5 and 29–33 and paclitaxel (25 mg/m²/day) was administered twice weekly for 12 cycles. This treatment led to the development of severe acute skin (grade 3: 22%) and mucosal toxicity (grade 3: 57%). Therefore, we modified the CRT regimen, reducing the cisplatin and paclitaxel doses. Reduction resulted in significant improvement of feasibility. However, this did not apply to the group given parallel doses of docetaxel, who developed grade 3 skin toxicities after 3–4 doses of 10 mg/m² docetaxel

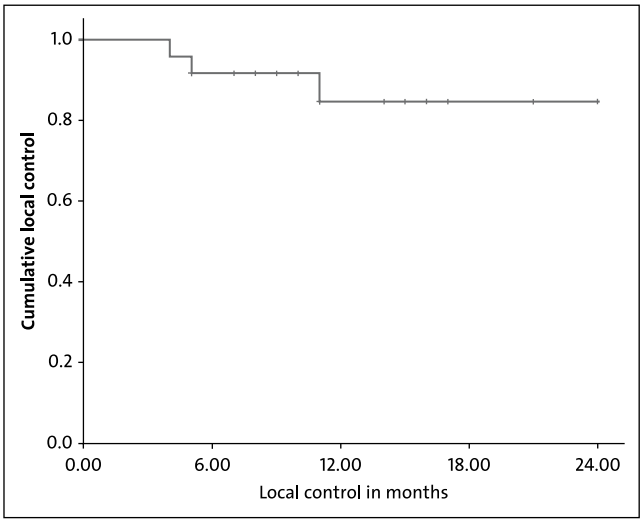

Figure 3. Local control in all 25 patients.

Abbildung 3. Lokale Kontrolle bei allen 25 Patienten.

once weekly, as pointed out previously for low dose monotherapy [8].

The introduction of a taxane in the ICT was based on the observation that the addition of docetaxel to the PF regimen led to improvement of response rate [11, 17], local control [9, 18, 19], and overall survival. This aspect is supported by four randomized phase III trials and one meta-analysis [4, 6, 9, 16, 24]. The survival advantage 2 years after treatment was 20%. The distant metastasis rate remained unchanged. Therefore, treatment was postulated to have a predominantly local effect. But in the light of increasing hematotoxicity of the triple therapy compared with the doublet therapy, the role of 5-FU has to be reassessed. We decided to omit 5-fluorouracil from the regimen because it induces mucosal toxicity and cumulative myelosuppression. Findings from the TAX 324 and S0216 trials support this decision. In the TAX 324 study [18, 19], only 73% and in the S0126 trial [2] 68% of patients completed treatment as planned and 5.4% of patients died due to treatment-related causes. The DeLOS II trial was also modified due to excessive toxicity and is now being performed using 3 cycles of TP induction chemotherapy. Data from an analysis from Tribius et al. suggest the omission of 5-FU during radiotherapy does not compromise the effect of a cisplatin-containing CRT [21, 22].

After 2–3 cycles of docetaxel/platin and paclitaxel/platin have been administered, the doses proposed in this regimen (250 mg/m² cisplatin or equivalent and 160 mg/m² paclitaxel plus 75 mg/m² docetaxel) are not significantly different from those used in the modified TPF regimen.

In addition to disease control, the improvement of the long-term effect of CRT on swallowing function is important. The DeLOS group is currently verifying a long-term ICT followed by a cetuximab-containing RT. An alternative is the improvement of accuracy of target volume definition, dose delivery on critical structures, and the modification of RT fractionation. Dose delivery at swallowing muscles has been tagged as a critical point [5, 14]. Preventive swallowing exercises are helpful perhaps, but function preservation has its limitations due to organ infiltration. Thus, organ preserving surgical procedures without CRT also result in significant swallowing problems [15].

In the end, the question of whether one cycle of induction chemotherapy will suffice to achieve a predictable response to subsequent chemoradiotherapy remains to be clarified. This assumption is supported by the findings of a study performed at the University of Michigan [23], which investigated the prognostic relevance of one induction cycle for early tumor response. The induction regimen made it possible to keep the rate of secondary laryngectomy below 10%.

Although the number of patients in our population is too small and the follow-up period too short to draw reliable conclusions, the fact that only 2 patients had persistent local tumor and local recurrence after chemoradiotherapy is very promising.

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