HYPERFRACTIONATED ACCELERATED RADIOTHERAPY IN COMBINATION WITH WEEKLY CISPLATIN FOR LOCALLY ADVANCED HEAD AND NECK CANCER

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Abstract: Background. The purpose of this study was to determine the feasibility and efficacy of hyperfractionated accelerated radiotherapy (HFRCB) combined with simultaneous chemotherapy with weekly cisplatin (CDDP) in locally advanced inoperable head and neck cancer.

Methods. From August 1999 to December 2002, 37 patients (median age, 59 years) with Union Internationale Contre le Cancer stage III (n = 2) and stage IV (n = 35) squamous cell cancer of the oropharynx and hypopharynx were treated in a prospective phase I/II trial. Concomitant boost radiotherapy (1.8 Gy, days 1–38 and 1.5 Gy boost, days 22–38, twice daily with at least a 6-hour interval; total dose 69.9 Gy) and simultaneous cisplatin, 40 mg/m² weekly, were given.

Results. The median treatment duration was 42 days (range, 38–46 days). Toxicity was manageable, with neutropenia grade II/IV and thrombocytopenia grade II in seven and one patients, and mucositis grade II/IV in 27 and five patients, respectively. Chemotherapy was restricted to four weekly applications in 29 patients mainly because of mucosal toxicity with a median dose intensity of 160 mg/m² (0–200) of cisplatin in 5.5 weeks. With a median follow-up of 28 months for living patients, the 2-year overall survival rate was 67%. The median overall and relapse-free survival times were 36 and 31 months, respectively.

Conclusion. HFRCB in combination with weekly cisplatin achieves a high rate of locoregional control and survival. Four weekly cycles of 40 mg/m² cisplatin seem to be the dose limit for most patients. © 2004 Wiley Periodicals, Inc. Head Neck 27: 36–43, 2005

Keywords: advanced head and neck cancer; phase I/II trial; concurrent radiochemotherapy; weekly cisplatin; concomitant boost radiotherapy

Local control is a major issue in treating patients with advanced head and neck cancer. At present, 40% to 60% of patients are at risk of dying because of locoregional recurrence compared with 20% to 30% who will die from distant metastases. Local recurrence that is not completely resectable is fatal and causes devastating clinical problems.

Attempts have been made to increase local control and disease-free survival in patients with advanced head and neck cancer over that seen with standard treatment with conventional fractionated radiotherapy. Several controlled randomized trials published since 1990 showed significant improvement of local control by intensified radiotherapy1–5 and of overall survival by combined radiochemotherapy.6–11
According to two meta-analyses, adding chemotherapy to locoregional therapy for head and neck squamous cell cancer produces an absolute gain in overall survival of about 5% at 5 years. The results of both meta-analyses suggest that simultaneous chemotherapy and radiotherapy is the optimal way to combine these modalities.

Concurrent radiotherapy and chemotherapy causes the problem of rather high acute toxicity in patients usually seen in reduced general condition. Some protocols contained scheduled treatment breaks that provided time for the patient to recover from side effects but probably also for the tumor to regrow.

Our intention was to establish a radiochemotherapy protocol based on hyperfractionated accelerated radiotherapy that has proven to be effective even without adding chemotherapy. Accelerated repopulation is thought to start in squamous cell cancer after the third week of radiotherapy, and tumor control is adversely related to the duration of the entire treatment. Considering this, the concept of concomitant boost therapy is convincing as total treatment time is shortened by applying a second daily fraction to all sites of macroscopic tumor starting at a time when accelerated repopulation is suspected.

We gained experience with concomitant boost radiotherapy while taking part in a German randomized multicenter trial comparing radiotherapy alone with radiotherapy and additional chemotherapy with carboplatin/5-fluorouracil. After recruitment had stopped, a phase I/II protocol was started at our institution with the same radiotherapy scheme but with cisplatin administered on a weekly base.

Cisplatin induces tumor responses as a single agent and has proven activity as radiosensitizing agent. It is commonly used in squamous cell cancer of the upper respiratory, aerodigestive, and genitourinary tracts, alone and in combination with radiotherapy, and has a toxicity profile that differs from that of radiotherapy. Concurrently with radiation, cisplatin was applied at a dose of 20 mg/m² weekly in a randomized Eastern Cooperative Oncology Group study without benefit. The Radiation Therapy Oncology Group tested a simultaneous radiochemotherapy with 100 mg/m² every 3 weeks but reached a dose intensity for cisplatin of only 60% of the scheduled dose. We decided to choose a weekly application of cisplatin that could allow adapting the intensity of the treatment to the individual tolerance of each patient to avoid interruptions of radiotherapy. The dosage of 40 mg/m² per week was used from the Gynecology Oncology Group radiochemotherapy protocol for cervical cancer.

**PATIENTS AND METHODS**

**Patient Selection.** Between August 1999 and December 2002, patients with histologically proven squamous cell cancer of oropharynx and hypopharynx whose disease was considered inoperable because of tumor extent and/or medical reasons were enrolled and treated according to a prospective phase I/II protocol (see Figure 1). Pretreatment staging procedures included medical history and general physical examination. Local tumor extension was assessed by rigid endoscopy of the oropharynx, hypopharynx, and larynx under general anesthesia, CT (or MRI) of head and neck, and ultrasonography of cervical lymph nodes. Distant metastases and coincident tumor of the upper aerodigestive tract were ruled out in all cases by endoscopy, chest x-ray, ultrasonography of the abdomen, bone scan, and a double-contrast esophagogram. Complete blood cell count, serum electrolytes, liver enzymes, and renal function tests (serum creatinine and creatinine clearance) were checked, and a pretreatment audiogram was done. Appropriate dental treatment including extractions was completed before the start of radiotherapy. Informed consent was obtained from each patient. The local ethics committee approved the study.

**FIGURE 1.** Time schedule for concomitant boost radiochemotherapy. CDDP, cisplatin.
Radiotherapy.

Treatment Technique. Three-dimensional (3D) conformal treatment planning after mask or bite block fixation based on a planning CT was routinely performed. The primary tumor and bilateral draining lymphatics above the clavicles were treated with five fractions per week over 5.5 weeks (days 1–38) with a single dose of 1.8 Gy up to a total dose of 50.4 Gy. Starting in the fourth week of treatment, an additional radiotherapy session per day was given as concomitant boost (days 22–38). The time interval between the two daily sessions had to be at least 6 hours. The boost volume covered the primary tumor and involved neck nodes. The dose prescription for boost radiation was 1.5 Gy/day up to 19.5 Gy, resulting in a total tumor dose of 69.9 Gy; 5- to 6-megavolt photons of a linear accelerator were used.

The cumulative dose to the spinal cord was not to exceed 46 Gy, and because of 3D-conformal treatment planning, the spinal cord was never exposed to the entire dose per fraction.

Chemotherapy. Patients were given cisplatin, 40 mg/m², administered intravenously once a week over 30 minutes. Comedication encompassed prophylactic antiemetics (granisetron and dexamethasone), osmodiuresis, and hydration with 1 liter of saline and 1 liter of glucose 5% before and again after cisplatin. Creatinine clearance from urinary sampling was checked and had to be normal before each application.

Application of cisplatin was delayed or stopped in case of severe mucositis, leukocyte count < 2.0/nL, or thrombocytes < 100/nL to prevent treatment breaks of radiotherapy.

Supportive Care. All patients were seen by an expert dentist, and necessary interventions were performed before the start of therapy. During therapy, patients were regularly assessed and repeatedly instructed to do intensive mouthwashes. Oral candidiasis was consequently treated with local nystatin suspension or systemic ketoconazole.

As we had learned from our previous experiences with concomitant boost radiation, an enteral feeding tube (percutaneous endoscopic gastrostomy) was placed at the beginning of treatment in almost all patients to guarantee sufficient nutrition and prevent weight loss during therapy and thereafter. Hemoglobin levels were kept above 12 g/dL during treatment.

Evaluation of Response. In addition to clinical investigations, CT of the head and neck region was performed 6 weeks after the end of radiochemotherapy.

Complete remission was defined as no evidence of tumor in all previously involved lesions. Partial remission was defined as more than 50% reduction of tumor volume (primary and lymph node metastases).

In the case of bulky or persisting lymph node metastases, neck dissection was recommended, and control endoscopy with biopsy of the primary tumor region was done beforehand. Endoscopic evaluation was also done if residuals of the primary tumor were seen and further options for local therapy (eg, laser resection or brachytherapy) existed.

Objectives and Statistical Evaluation. Patients were analyzed according to intention to treat. Progression-free survival and overall survival were estimated from Kaplan-Meier curves, with time to event beginning at the start of treatment. Patients dying because of intercurrent disease or treatment-related toxicity were not censored in this phase I/II study but were censored for calculation of locoregional control.

RESULTS

Patient Characteristics. From August 1999 until December 2002, 37 patients (32 men and 5 women) were prospectively entered into the study. The median age was 59 years (range, 42–77 years).

Median Karnofsky performance score was 90% (70% to 100%). Patient characteristics are shown in Table 1, and distribution by T and N classification is shown in Table 2. Disease in all patients was inoperable because of locally advanced squamous cell carcinoma of the oropharynx (n = 21) or hypopharynx (n = 3), tumors involving both locations (n = 9), and even tumors extending into the nasopharynx (n = 4). Two patients had UICC stage III tumors, and 35 patients had UICC stage IV tumors.

The median follow-up was 24 months (range, 2–46 months) for all patients and 28 months (range, 7–44 months) for patients alive.
Compliance with Treatment and Toxicity. Thirty-one of the 37 patients were treated with concomitant boost radiotherapy. The range of totally delivered dose was 63.3 Gy to 71.4 Gy.

In two patients, the treatment had to be stopped after reaching a dose of 63.3 and 65.3 Gy and four and three cycles of cisplatin. Both patients died a few days later because of rapid deterioration of their general condition caused by sepsis and acute respiratory insufficiency. A treatment break of 5 days was necessary in one patient because of cardiac ischemia with pre-existing heart disease.

In four patients treated with concomitant boost radiotherapy, chemotherapy was stopped after the first or second cycle, and in five patients it was stopped after the third cycle because of toxicity, compliance problems, or patient refusal; 16 patients received four cycles, and five patients received five cycles.

One patient refused chemotherapy altogether. The median dose intensity of cisplatin, therefore, was 160 (range, 40–200) mg/m² in 5.5 weeks.

In three patients, the concomitant boost scheme was not applied, because of the large extension of the primary tumor and lymph node metastases. In these patients, the target volume for the boost series had nearly the same extent as the main series, and the concomitant boost was regarded as too toxic. These patients, together with two additional patients who denied concomitant boost irradiation because of mucositis and one patient who showed bad compliance, were treated with 2.0 Gy per single fraction up to a total dose of 70 Gy. The six patients eventually treated by conventionally fractionated radiotherapy received one (n = 1), three (n = 3), or five (n = 2) cycles of chemotherapy.

The median treatment duration was 42 days (range, 38–58 days) for all patients and 42 days (range, 38–46 days) for patients treated with concomitant boost radiochemotherapy compared with the minimum 38 days scheduled. Prolongation resulted mainly from bank holidays and treatment not starting on Mondays.

Toxicity. Toxicity was scaled according to CTC/RTOG criteria. Oral and pharyngeal mucositis were the major problems during therapy as expected. Twenty-seven of 37 patients had grade III and five of 37 patients had grade IV mucositis develop, requiring narcotics for analgesia at the end of treatment until regeneration of epithelium.

Despite this, loss of body weight was kept to less than 10% in six of 32 and less than 5% in 25 of 32 patients who had already been provided with a gastric feeding tube before the onset of mucositis.

Chemotherapy was well tolerated with prophylactic antiemetics, with no grade II or higher nausea at all. Leukopenia grade II, grade III, and grade IV were observed in seven, six, and one patients, with fever and need for empiric antibiotics in three cases. Four patients had pneumonia without leukopenia during and after treatment.

One patient died from neutropenic sepsis and disseminated intravascular coagulation; another died because of acute respiratory distress syndrome without changes in blood cell count. Thrombopenia was rare, with two cases of grade II and one grade III and grade IV each.

Red blood cell transfusions were given to keep hemoglobin levels above 12 g/dL; several patients required transfusion once during combined-modality treatment.

Renal toxicity was low and transient with elevated serum creatinine levels grade I/II in two cases, each during neutropenic fever. Reduction

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics.</th>
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<tbody>
<tr>
<td>Patient characteristics</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Karnofsky score, %</td>
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<tr>
<td>Sex</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Primary site</td>
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<tr>
<td></td>
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<tr>
<td>UICC stage</td>
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Abbreviation: UICC, Union Internationale Contre le Cancer.
Note: Values represent number of patients, except as otherwise stated.

<table>
<thead>
<tr>
<th>Table 2. Distribution by T and N classifications.</th>
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<tbody>
<tr>
<td>T0</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>N0</td>
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<tr>
<td>N1</td>
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</tbody>
</table>

Simultaneous Hyperfractionated Accelerated Radiotherapy Plus Cisplatin
of creatinine clearance to less than 60 mL/minute with normal serum creatinine was seen in six patients, and chemotherapy with cisplatin was stopped for this reason.

Laryngitis grade II and III that resolved after treatment with corticosteroids was seen in three patients with oropharyngeal/hypopharyngeal cancer during chemoradiation. One patient had edema of supraglottic larynx develop 11 months after treatment, requiring tracheostomy.

Late toxicity consisted predominantly of xerostomia (four patients, grade III; 15 patients, grade II; nine patients, grade I; two patients, none), depending on the target volume in the main and the boost series and the possibility of sparing the parotid glands by radiotherapy technique.

Otoxicity grade II and IV occurred in one patient each.

Two patients had osteoradionecrosis of the mandible develop, one patient 5 months after therapy and the other 7 months (tumor-bearing side) and 29 months (contralateral side) after therapy.

Response. Response to therapy was assessed 6 weeks after the end of radiochemotherapy by CT and clinical investigation.

At this time, CT revealed complete remission of primary and lymph node metastasis in six patients; the others had CT abnormalities at the primary tumor site, even without clinically detectable tumor. Repeated CT showed further regression of these lesions, and complete remissions were documented in another 21 patients. Sixteen patients with suspected residual disease at the primary tumor site had endoscopic restaging with biopsies 2 to 9 months after the end of therapy without evidence of residual tumor and negative biopsy results. Persistent lymph node metastases were seen, especially in cases with initially central necrosis. Three of these patients with complete remission of the primary tumor were referred for a secondary neck dissection, and tumor cells were still found in two specimens. Another patient had secondary resection of the primary tumor and neck node dissection because of residual disease but died of distant metastases 22 months later.

Overall Survival and Progression-free Survival. Median overall survival was 36 months, and 2-year survival was 67% (Figure 2). Median relapse-free survival was 31 months, and 2-year relapse-free survival was 58% (Figure 3).

Nineteen patients are still alive without clinical evidence of locoregional recurrence or distant metastases after a median follow-up of 28 months. One patient is alive with recurrence at the neck 34 months after the end of radiotherapy and 27 months after neck dissection.

Thirteen patients died of disease, four of them with rapid progression after therapy. Two patients died of unrelated illness with complete remission of tumor.

Failure at the primary site was seen in seven cases and at the neck in four cases, with combined failure in one case.

Although nodal recurrence could be successfully treated by neck dissection in three cases, all patients with recurrence at the primary site died despite salvage therapy (laser resection and chemotherapy). Distant metastases were seen in
DISCUSSION
The purpose of this study was to determine the feasibility and efficacy of simultaneous radiochemotherapy with accelerated hyperfractionated concomitant boost radiation and weekly cisplatin.

The regimen showed practicability and promising results in a patient collective with irresectable, locally advanced head and neck cancer. The prescribed radiotherapy dose was administered in all but three patients without treatment breaks. A negative effect on local control by treatment prolongation is known even if this negative effect can be reduced by addition of full-dose chemotherapy. However, only 25 of 37 patients received the treatment as specified in the protocol: concomitant boost and at least three cycles of weekly cisplatin. Similar experiences were reported in the RTOG trial on concurrent radiochemotherapy, highlighting the problems encountered in this patient population.

We present the results as intention to treat for all patients, because feasibility was the primary end point in this phase I/II trial.

Chemotherapy in our protocol was given to enhance the effects of local radiotherapy. However, five cycles of chemotherapy with cisplatin, 40 mg/m² per week, were not tolerable in most patients parallel with concomitant boost radiotherapy because of confluent mucositis in the fifth week. Seven of 37 patients received five cycles, 17 of 37 patients received four cycles, and five of 37 received three cycles. Because we had two treatment-related deaths in the beginning of the protocol, we grew cautious and did not treat patients who had reduced physical condition and extensive mucositis with full-dose chemotherapy. We found that four weekly cycles of 40 mg/m² cisplatin can be given safely together with concomitant boost radiotherapy, and this can be managed with adequate supportive care, especially in terms of analgesia and nutrition.

The cumulative dose of 160 mg/m² in 5 weeks is somewhat lower than the RTOG scheme with 100 mg/m² every 3 weeks, but this dosage was tested only in combination with conventionally fractionated radiotherapy.

There are advantages in using a weekly schedule. First, a putative radiosensitizing effect of cisplatin can be better exploited by repeated applications. Others have used cisplatin predominantly for radiosensitizing effects and applied a low dose every day before the radiotherapy session.

Second, this application is practicable and well tolerated with respect to chemotherapy-related side effects such as hematotoxicity, nephrotoxicity, neurotoxicity, and nausea. The rather high rate of acute mucosal toxicity with nearly 100% grade III was caused by our policy to avoid treatment breaks of radiotherapy (allowing mucosal recovery) and intensifying supportive care instead. For this reason, most patients were hospitalized at least during the concomitant boost phase of treatment.

Comorbid illnesses also related to chronic tobacco and alcohol abuse (eg, chronic obstructive lung disease and heart disease) were present in many patients. Patients usually are initially seen in a compensated status despite these comorbidities, and it is not always easy to determine the risk of deterioration during intensive treatment. A weekly chemotherapy regimen offers the possibility to “titrate” the cumulative dose of chemotherapy in each individual patient and, therefore, could be applied even when full-dose chemotherapy seemed to be inadvisable. Nevertheless, we had two cases of fatal pulmonary complications and another four cases of bronchopneumonia without association with neutropenic episodes, reflecting the problem of underlying lung disease and impaired mucous clearance during radiotherapy.

Compared with the weekly use of cisplatin (40 mg/m²) concurrently with radiotherapy according to the GOG protocol for cervical cancer, the same chemotherapy together with concomitant boost radiation for head and neck cancer seems to be much more aggressive. This might be explained by the difference in radiotherapy itself, because accelerated hyperfractionated radiotherapy produces more severe acute side effects than conventional fractionation. In addition, the mucosal barrier in the oral cavity and pharynx might play a more important role against infections than it does in the pelvis. Another important difference is, of course, the patient collective, with usually younger healthy women with cervical cancer instead of multimorbid elderly patients with head and neck cancer.

Initial response to therapy seemed relatively low, but assessment was done 6 weeks after the end of therapy by CT and often revealed residual masses at the tumor site without clinical correlate. These persistent changes at the primary
tumor turned out to be no vital tumor in biopsies carried out later. In contrast, large neck node metastases, especially with central necrosis, usually showed no complete regression after radiochemotherapy. We recommend considering elective secondary neck dissection for initial N2/3 stage, as well as for persistent or recurrent neck node disease.  

Until now, only two patients had distant metastases develop, which is less than the commonly assumed rate of about 20%. This is probably an effect of the low number of patients in our study. A definitive effect of chemotherapy on the incidence of distant metastases is still not proven, even with full-dose combination chemotherapy. The protocol was initiated at our institution after we had taken part in a randomized phase III trial testing the additional benefit of chemotherapy with concomitant boost radiotherapy. The results of this study were published in 2001 and showed an improvement in locoregional control from 45% to 51% and overall survival from 39% to 48% after 2 years by adding chemotherapy to hyperfractionated accelerated radiotherapy for irresectable oropharyngeal cancer. Grade III/IV mucosal toxicity was enhanced from 52% with radiation alone to 68% with radiochemotherapy. Grade III/IV mucositis in our study was more pronounced with 86%. But the German multicenter trial also randomized for prophylactic use of filgrastim, which showed reduced mucosal toxicity but led to a decreased locoregional control and was, therefore, abandoned. Grade III/IV mucosal toxicity is 63% during concomitant boost radiotherapy alone and during combined-modality treatment with conventional fractionated.

Sixty-seven percent overall and 58% relapse-free survival of this phase I/II trial at 2 years compare well with yet published multicenter trials testing hyperfractionated accelerated radiation together with chemotherapy and with our own previous data from controlled trials (see Table 3).

Concomitant boost radiotherapy with weekly application of cisplatin is one arm of the most recent German multicenter trial for advanced head and neck cancer started in January 2004.

**CONCLUSION**

The strategies used during the past decades to improve outcome for patients with locoregionally advanced head and neck cancer include altered fractionation and combined radiochemotherapy. These intensified treatment schemes not only enhance the possibility for local control but also

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**Table 3. Simultaneous radiochemotherapy for advanced head and neck cancer.**

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Site</th>
<th>Therapy</th>
<th>Locoregional control, %</th>
<th>Disease-free survival, %</th>
<th>Overall survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanchiz†</td>
<td>859</td>
<td>11% N</td>
<td>SF-RT 60 Gy</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>29% O</td>
<td>HFRT 70.4 Gy</td>
<td>37*</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50% HL</td>
<td>SF-RT 60 Gy + 5FU</td>
<td>n.s.</td>
<td>31* (10 y) 42* (10 y)</td>
</tr>
<tr>
<td>Brizel‡</td>
<td>122</td>
<td>6% N</td>
<td>HFRT 75 Gy</td>
<td>44</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50% O</td>
<td>HFRT 70 Gy + P/5FU</td>
<td>70* (3 y)</td>
<td>61* (3 y) 55* (3 y)</td>
</tr>
<tr>
<td>Wendt§</td>
<td>298</td>
<td>42% O</td>
<td>ART/SC 70.2 Gy</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36% HL</td>
<td>ART/SC 70.2 Gy + P/5FU/LV</td>
<td>36* (3 y)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Calais††</td>
<td>226</td>
<td>100% O</td>
<td>SF-RT 70 Gy</td>
<td>42</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SF-RT 70 Gy + Carbo/FU</td>
<td>66* (3 y)</td>
<td>42* (3 y)</td>
<td>51* (3 y)</td>
</tr>
<tr>
<td>Budach††</td>
<td>384</td>
<td>60% O</td>
<td>ART 77.6 Gy</td>
<td>45</td>
<td>n.s.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>32% H</td>
<td>ART 70.6 Gy + 5FU/MMC</td>
<td>61* (2 y)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Adelstein‖</td>
<td>295</td>
<td>73% O</td>
<td>SF-RT 70 Gy</td>
<td>45</td>
<td>23</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>18% H</td>
<td>SF-RT 70 Gy + P</td>
<td>n.s.</td>
<td>37</td>
</tr>
<tr>
<td>Staar‡‡</td>
<td>240</td>
<td>74% O</td>
<td>HFRCB 69.9 Gy</td>
<td>45</td>
<td>39</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>26% H</td>
<td>HFRCB 69.9 Gy + Carbo/5FU</td>
<td>51 (2 y)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Jeremic‡‡</td>
<td>130</td>
<td></td>
<td>HFRRT 77 Gy</td>
<td>49</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HFRRT 77 Gy + daily P</td>
<td>n.s.</td>
<td>n.s.</td>
<td>68* (2 y)</td>
</tr>
<tr>
<td>Olmi‡‡</td>
<td>192</td>
<td>100% O</td>
<td>SF-RT 66-70 Gy</td>
<td>23</td>
<td>40</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HFR/SC 64-67.2</td>
<td>n.s.</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SF-RT 66-70 Gy + Carbo/5FU</td>
<td>42* (2 y)</td>
<td>51 (2 y)</td>
<td>51 (2 y)</td>
</tr>
</tbody>
</table>

Abbreviations: N, nasopharyngeal cancer; O, oropharyngeal cancer; H, hypopharyngeal cancer; L, laryngeal cancer; n.s., not stated; SF-RT, standard fractionation radiotherapy; HFRT, hyperfractionated radiotherapy; ART, accelerated radiotherapy; HFRCB, hyperfractionated accelerated radiotherapy; SC, split course; P, cisplatin; MMC, mitomycin C; Carbo, carboplatin.  
*Statistically significant.
the risk of treatment breaks and interruptions because of acute toxicity.

Accelerated hyperfractionated radiotherapy in combination with weekly cisplatin can be administered with acceptable morbidity in patients with good performance status and achieves a high rate of locoregional control and survival. Four weekly cycles of 40 mg/m² cisplatin seem to be the dose limit for most patients.

REFERENCES