Abstract. Background: This study was designed to evaluate the concomitant use of weekly docetaxel and hyperfractionated radiotherapy for the treatment of head and neck cancer (HNC). Patients and Methods: Twenty-five patients with advanced squamous cell HNC were treated with hyperfractionated radiotherapy (72 Gy at 1.2 Gy twice per day) and weekly chemotherapy with docetaxel (10 mg/m²). Results: Toxicity was significant, with grade 2 to 4 mucositis observed in 100% and lymphopenia in 84%. Seventeen patients (68%) received the full chemotherapy regimen as planned. The initial overall response rate was 88.0%, while the complete response rate was 68.0%. At a median follow-up period of 10 months, the 2-year Kaplan-Meier projected overall survival was 47.3%, and the cause-specific survival was 81.8%. Conclusion: This study demonstrated that hyperfractionated radiotherapy with weekly docetaxel achieved better initial response than conventional radiotherapy. In addition, the acute toxicity of this regimen was within the acceptable limits of severity.

The majority of patients with head and neck squamous cell carcinoma (HNSCC) present with locoregionally advanced disease, associated with a poor prognosis despite treatment by surgical resection, radiotherapy, or both. As a result, new treatment strategies that incorporate systemic agents, with the goal of organ preservation and optimal disease control, have become a major focus of clinical investigations in head and neck cancer (HNC). A meta-analysis provided level I evidence of survival benefits under concurrent chemoradiotherapy (1). Various chemotherapeutic drugs that have shown activity in the treatment of HNSCC have been combined with radiotherapy. Cisplatin is the agent that has been studied the most, at various doses and schedules (2). On the other hand, docetaxel is one of the most active agents for HNSCC (3) and is believed to be a radiosensitizer (4). Docetaxel has been reported to be an effective anticancer agent against HNSCC. Response rates of 21-42% were reported following therapy with docetaxel as a single agent in patients with locally advanced, recurrent and/or metastatic HNSCC (5). The drug promotes the polymerization and stabilization of microtubules, thus, leading to an accumulation of cells at the G2/M boundary, which is relatively the most radiosensitive phase of the cell cycle (6-8). When it was first introduced, docetaxel was administered once every 3 weeks; however, weekly administration now appears to offer several advantages in terms of toxicity, especially regarding myelosuppression. In addition, weekly administration also increases the chance of enhancing the effect of radiotherapy (9).

Hyperfractionated radiotherapy is considered to be one of the techniques for achieving better treatment results than with conventional radiotherapy. Theoretically, this alternative could make it possible to raise the total radiation dose without increasing the incidence of late toxicities or prolonging the overall treatment time (10). Moreover, randomized clinical trials revealed that hyperfractionated radiotherapy was superior to conventional radiotherapy for the treatment of HNC, especially regarding local control (11, 12).

Regarding the effects of combined docetaxel and radiotherapy, Airolidi et al. conducted a phase I and phase II study on cases of unresectable HNSCC and concluded that therapy with carboplatin and docetaxel administered concurrently with conventional radiotherapy was a feasible and effective treatment method for unresectable HNSCC (13). However, to our knowledge, there have been no studies on chemoradiotherapy with weekly docetaxel and hyperfractionated radiotherapy for advanced HNC. Under these circumstances, a study of concurrent docetaxel based chemotherapy and hyperfractionated radiotherapy was conducted on HNSCC patients.
Patients and Methods

Patients. Consecutive patients with histologically proven locally advanced HNSCC were investigated. All patients had their medical histories taken and underwent a physical examination including endoscopic examination, fiberscopy, chest X-ray or chest computed tomography (CT), CT and magnetic resonance image (MRI) of the head and neck. The patients had either previously untreated HNSCC or had been previously treated with radiotherapy and/or chemotherapy. Patients were staged according to the International Union Against Cancer staging system the treatment requirements were based on the Eastern Cooperative Oncology Group (ECOG) criterion performance status of less than two.

Radiotherapy. Radiotherapy was delivered with 4 MV photons. It was initially applied to a large field covering the entire primary site, including the regional lymph node area. After 40.8 Gy, of prophylactic nodal irradiation was completed, the field was then reduced to the area of the clinical tumor volume with a margin of 1 cm. In this study, the hyperfractionated radiotherapy consisted of 1.2 Gy per fraction; two fractions per day were delivered more than 6 h apart, 5 days per week. The total dose was 72 Gy. The mean overall treatment time was 43 days.

Chemotherapy. The patients received six or seven cycles of chemotherapy given concurrently with radiotherapy every week. Chemotherapy, which consisted of docetaxel, was given as a weekly 2-h bolus of 10 mg/m² of the body surface area and was administered 30 min before radiotherapy. The patients receiving this chemotherapy regimen were hospitalized. The patients were monitored at least weekly during their treatment, in an effort to manage treatment-induced adverse effects, particularly mucositis and myelosuppression.

Evaluation. The initial response was evaluated by either a physical examination, a fiberscopic examination and CT or MRI at 6 weeks after the end of chemoradiotherapy. In addition, flurodeoxyglucose positron emission tomography (FDG PET) was administered in all patients. A complete response (CR) was defined as the disappearance of all clinically evident tumors and no new disease. A partial response (PR) was defined as a >50% reduction in the sum of the products of perpendicular tumor measurements and no new disease. Stable disease (SD) was defined as less than a partial response and progressive disease (PD) was defined as a >25% increase or new sites of disease. After completion of the therapy, follow-up evaluations were performed at monthly intervals for the first year and then every other month for the second year. CT and/or MRI were performed every 3, 6, 9, 12 months and every 6 months, respectively. The overall and cause-specific survival rates were assessed using the Kaplan-Meier method starting from the date of treatment initiation. Toxicity was evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Measurement of tumor volume. The tumor volumes were measured with the Eclipse Treatment Planning System (Varian Medical Systems, USA) based on the treatment planning CT. The volume of the primary tumor and metastatic lymph nodes were measured all together. In cases in which artifacts derived from the dentures precluded a delineation of the tumor, the physical examination and diagnostic MRI findings were referred. The sum of the volume of each node in N2 or N3 disease was then estimated and analyzed.

Results

Patient population. Between March 2003 and November 2005, 25 patients were enrolled in the study. The clinical characteristics of these 25 patients and their tumors are detailed in Table I. Nodal metastases were present in 84% of the patients. Sixty-eight percent of the patients had advanced nodal disease (stage N2 or N3), 76% of these had huge primary tumors (stage T3 or T4). Fourteen patients had stage IV A, five patients had stage IV B and three patients had stage III disease.

Toxicity. No fatal treatment toxicity was observed. The acute toxicities, including mucositis, hematological and non-hematological toxicities, are summarized in Table II. No patient developed hypersensitivity reactions, either during or

### Table I. Patient characteristics.

<table>
<thead>
<tr>
<th>Age; median in years</th>
<th>64.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>23</td>
</tr>
<tr>
<td>female</td>
<td>2</td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
</tr>
<tr>
<td>oropharynx</td>
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</tr>
<tr>
<td>hypopharynx</td>
<td>8</td>
</tr>
<tr>
<td>larynx</td>
<td>8</td>
</tr>
<tr>
<td>oral cavity</td>
<td>1</td>
</tr>
<tr>
<td>T1</td>
<td>0</td>
</tr>
<tr>
<td>T2</td>
<td>2</td>
</tr>
<tr>
<td>T3</td>
<td>1</td>
</tr>
<tr>
<td>T4</td>
<td>1</td>
</tr>
</tbody>
</table>

| N0       | 0 | 2 | 1 | 1 |
| N1       | 0 | 1 | 2 | 1 |
| N2       | 0 | 2 | 7 | 3 |
| N3       | 1 | 0 | 2 | 2 |

### Table II. Acute toxic effects of treatment.

<table>
<thead>
<tr>
<th>Grade</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Leukopenia</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>7</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Hemoglobinemia</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>15</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>9</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>10</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related pain</td>
<td>14</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>
immediately after docetaxel infusion. Oral and pharyngeal mucositis were the major problems during therapy, as expected. Although all patients had grade II/III acute mucositis, no grade IV mucositis was observed. Sixteen out of 25 patients developed grade III mucositis, thus, requiring medication for analgesia at the end of treatment until the regeneration of epithelium. Seventeen patients (68%) received the full chemotherapy as planned. Five out of 25 patients received seven cycles, 12 patients received six cycles, 1 received five cycles, 4 received four cycles and 3 patients received three cycles. Patients who demonstrated a severely deteriorated physical condition and extensive mucositis were not treated. Two patients did not receive the whole radiotherapy, because their general condition deteriorated due to tumor growth. The radiotherapy was completed in the other patients without interruption.

Response and survival. Table III shows the response rates (RR) and the CR rate, regarding primary lesions, lymph node metastases and loco-region at the end of radiotherapy. Twenty-one out of 25 patients demonstrated CR in the primary lesion. A clinical CR was achieved in the neck in 14 out of the 21 assessable patients with neck nodes identified at presentation. The CR rate of the primary lesion was superior to that of neck metastases. A neck dissection was performed in 2 out of 8 patients with clinical evidence of residual adenopathy after chemoradiotherapy. Both patients undergoing a neck dissection had no residual evidence of disease in the neck. The cases were stratified by T-stage and N-stage. Although not statistically significant, the CR rates for the T1-3 stage cases were higher than for the T4 cases. The responses of chemoradiotherapy in N2b or more nodal disease were worse than for N1 or N2a nodal disease, but the difference was not statically significant either. These results are detailed in Table IV.

Among the 17 patients with CR, recurrence occurred in seven patients. The lymph node was the most common location of recurrence (in 4 patients). The primary site was involved in 2 patients and distant metastases were observed in 3 patients. The cases were stratified according to the primary lesion. Although not statistically significant, the initial response in the hypopharynx was worse than in the other lesions. Eight patients evaluated in this study died; five from disease progression or metastasis while the remaining three of intercurrent diseases, including secondary cancer. The 2-year overall and cause-specific survival rates of all patients were 47.3% and 81.8%, respectively. The relationship with the initial response and tumor volume is shown in Table V.

Discussion

Radiotherapy and chemotherapy may be combined in several ways in the treatment of head and neck carcinomas. The two treatments may be given simultaneously or with an alternating scheme. Radiotherapy may be delivered with conventional fractionation or with an accelerated or hyperfractionated regimen. Several randomized studies suggested an improvement in the survival with concurrent chemoradiotherapy (14-18). Radiotherapy with concurrent chemotherapy could be considered as the standard of care for the treatment of stage III and IV head and neck carcinomas, when nonsurgical treatment is planned.

Docetaxel is one of the active agents for head and neck malignancy. It has been used as a multi-agent chemotherapy in an induction setting. In three phase II studies of docetaxel-based regimens as induction therapy for patients with locally advanced HNSCC, the overall response rates
ranged from 93 to 100%, with CR rates of 40-63%. The primary toxicities were neutropenia and febrile neutropenia (19-21). Although it was an effective method, these regimens were not planned with concurrent chemo-radiation therapy due to associated acute toxicity. It was recently noted that neutropenia could be remarkably reduced by weekly administration. This method was used with concurrent chemoradiotherapy and it was considered to be theoretically effective. There are advantages in using a weekly schedule. First, a putative radiosensitizing effect of docetaxel can be better exploited by repeated applications. Others used docetaxel predominantly for radiosensitizing effects and applied a low dose every week before the radiotherapy session (22, 23). Second, this application is practicable and well-tolerated with respect to such chemotherapy-related side-effects as hematotoxicity, neurotoxicity and nausea. The rather high rate of acute mucosal toxicity (100% grade II or III) was caused by our policy of avoiding treatment breaks in radiotherapy, with intensified supportive care. For this reason, most patients were hospitalized during therapy. Several studies on chemoradiotherapy with weekly docetaxel for head and neck carcinoma have been published, but, to our knowledge, there are no previous studies on chemoradiotherapy with weekly docetaxel and hyperfractionation for the treatment of advanced HNC.

Many reports have suggested that dose escalation achieves an improved local control in radiotherapy for various malignancies (24, 25). Advances in biology have led to alterations in fractionated radiation therapy, including hyperfractionated radiotherapy, which has been performed since the 1980s to escalate the total dose without prolonging the overall treatment time. Furthermore, some randomized trials recently revealed the clinical effectiveness of altered fractionated radiotherapy for treating head and neck carcinomas, especially in their local control (11, 12). Fu et al. (11) reported the 2-year local control rate of hyperfractionation at 1.2 Gy per fraction totalling 81.6 Gy to be 54.4%, a statistically significant improvement over the conventional fractionation at 2 Gy per fraction totalling 70 Gy, which was 46.0%. In their study, further investigations were performed to compare two altered fractionated radiation therapies, accelerated fractionation according to the protocol of Wang et al. (26) and concomitant boost fractionation, with conventional fractionation. This comparison revealed only the concomitant boost fractionation to be superior to conventional fractionation. However, the concomitant boost fractionation had more severe late toxicity than that of conventional fractionation. These findings suggested that hyperfractionated radiotherapy was one of the best altered fractionated radiation therapies. However, no trials of hyperfractionation with weekly docetaxel have studied its effectiveness in the head and neck region according to sub sites. Akimoto et al. reported that altered fractionated radiotherapy was significantly superior to conventional radiation therapy, even regarding the overall survival rate of patients with hypopharyngeal carcinoma, although their altered fractionated radiotherapy was accelerated hyperfractionation, which caused more severe late toxicity than hyperfractionated radiotherapy (27).

The results of the present study show that concurrent chemo-radiotherapy using hyperfractionated radiotherapy combined with low-dose weekly docetaxel produced an overall response rate of 89.3% and a CR rate of 60.7%. Fujii et al. (28) reported the results including 60 Gy/30 fx of radiotherapy with 10 mg/m² of weekly docetaxel for stage III/IV head and neck carcinoma. The response rate and CR rate were 96.9% and 50%, respectively. Biete et al. used weekly docetaxel 20 mg/m² with conventional radiotherapy. The overall response rate was 88% and CR rate was 44% (29). Our response and CR rates were comparable to those of other reports. However, the CR rate in the hypopharynx was worst in the primary sites, and no significant site-specific differences in radiocurability were observed among the three sites. In addition, there were more patients with advanced nodal disease (N2b or more) among the hypopharynx patients.

Regarding primary lesions, the CR rate was 84.0% and regarding lymph node metastasis was 61.9%. It is more difficult to control neck node metastases than a primary lesion. In this study, the initial response in N1 and N2a stage were better than for N2b or more, but the difference was not statistically significant. Multiple neck node metastases were difficult to initially control in this protocol. Large neck node metastases, especially with central necrosis, usually showed no CR after chemoradiotherapy. Hence, we recommend an elective neck dissection for initial N2b-3 stage, when such lymph nodes are determined to be resectable. There were four patients who had clinical evidence of residual adenopathy with a complete response of the primary site. A neck dissection was performed in 2 of these patients with clinical evidence of residual adenopathy after chemoradiotherapy. Neither patient was observed with pathologically viable tumor cells.

As Dubben et al. (30) empirically stated, the tumor volume is regarded as the most reliable predictor of tumor control after RT. The importance of the tumor volume for local control after RT was also reported for various head and neck cancers (31, 32). Although Bentzen and Thames (33) stated that patient-to-patient variability in radiocurability and other factors also make the volume effect less pronounced than would be expected from a simple proportionality between them, the significance of other factors predictive of tumor radiosensitivity still remains controversial and radiocurability, in comparison to
the tumor volume has not been quantitated. The data from the present study were not sufficient to indicate that the tumor volume correlated with the treatment outcomes for patients undergoing targeted chemoradiotherapy. However, the mean tumor volumes in the CR and PR groups were significantly small. As a result, recommending this regimen to patients who initially presented with a huge tumor remains controversial.

Some patients developed grade 2 or higher hematological toxicity. Six out of 25 patients developed grade 2 or higher leukopenia and three out of the 25 developed grade 2 or higher neutropenia. The most common hematological toxicity was lymphopenia. Recent publications reported weekly applications of concomitant docetaxel and radiotherapy, which seemed to cause less neutropenia (9, 34). Lymphopenia was severe and caused pneumonia in other studies with weekly docetaxel at more than 20 mg/m. Docetaxel-induced interstitial pneumonia was also reported to increase by simultaneous lymphopenia. In this study, lymphopenia was mild. Only fourteen patients developed grade 3 or more lymphopenia. The lymphopenia did not disturb the schedule of chemoradiotherapy, but the mechanism of this toxicity is unclear. Although no grade 4 mucosal toxicity was observed, grade 3 mucosal toxicity occurred in 64.0% of the patients, similar to other reported data (35-37). Calais et al., (35) reported the results of a phase II study including 70 Gy/35 fx of radiotherapy with 20 mg/m² of weekly docetaxel for stage III/IV oropharyngeal carcinoma. The rate of grade 3 and 4 mucositis was 84%. In eight patients, six or seven cycles of chemotherapy with weekly docetaxel were not tolerable with concomitant hyperfractionated radiotherapy because of severe mucositis. However, no acute mucositis severe enough to cause an interruption of the radiation therapy occurred. We were therefore cautious and did not treat any patients who had a reduced physical condition or extensive mucositis. Aggressive follow-up care, hospitalization, prompt nutritional intervention and analgesia all played a critical role in maintaining the dose intensity of this treatment regimen and were in large part responsible for the success achieved. Two patients did not receive the whole protocol radiation therapy and died during this therapy. However, the reason for death was not toxicity. Their general condition rapidly deteriorated due to tumor growth.

The 2-year overall survival and cause-specific survival rates were 47.3 and 81.8%, respectively. Needless to say, the median follow-up duration of 8 months was not sufficient to allow for a reasonable evaluation of the long-term outcomes. However, our results seemed to be comparable to those of weekly docetaxel concurrent chemotherapy and radiation therapy. Although the patients evaluated in this study may have deceased for many different reasons, the overwhelming cause of death in this cohort was either distant metastatic disease or second primary neoplasms, and not due to a locoregional tumor. Other investigators who used similar aggressive locoregional treatments have made this same observation, and attention must now be focused on the prevention of such distant metastases. Appropriate intervention might include the use of additional multi-agent chemotherapy given as either induction or adjuvant treatment, or the use of other, nonchemotherapeutic systemic approaches. However, the complexity of these treatment regimens and their effect on patient compliance remain a significant concern.

In conclusion, this study demonstrated that hyperfractionated radiotherapy with weekly docetaxel achieved a better initial response. The acute toxicity of this regimen was also within the acceptable limits of severity. Based on the small number of patients and the short observation period of this study, we could not conclude that the docetaxel regimen offers any substantial survival or organ-sparing benefits.

References


