Quality-of-Life Assessment After Supradose Selective Intra-arterial Cisplatin and Concomitant Radiation (RADPLAT) for Inoperable Stage IV Head and Neck Squamous Cell Carcinoma

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**Objective:** To evaluate quality-of-life (QOL) aspects of an organ preservation intra-arterial chemotherapy and concomitant radiation protocol, RADPLAT.

**Design:** Nonrandomized phase 2B feasibility trial.

**Patients:** Fifty consecutive patients with inoperable stage IV head and neck cancer.

**Intervention:** Supradose selective intra-arterial cisplatin and concomitant standard radiation (RADPLAT).

**Measures:** Assessment with structured questionnaires before treatment and at 3, 6, and 12 months.

**Results:** Twenty-six patients were available for QOL assessment at 1 year (the “1-year QOL” group), as 16 patients died, 5 needed salvage surgery, and 3 were not available for interview (the “failure” group). Twelve-month results were mainly based on the first group. The functional well-being and head and neck scales showed a statistically significant improvement over time ($P < .001$). After 12 months, 21 patients (81%) returned to an oral diet, while 5 patients still needed tube feeding. For 23 patients (88%), the quality and strength of the voice was more or less normal. Of the 18 patients who were employed before their treatment, 10 were able to return to their job within 12 months. Xerostomia was reported by 17 patients (65%). Further detailed analysis showed statistically significant differences in pretreatment scores between the 1-year QOL group and the failure group, ie, physical well-being, functional well-being, and the head and neck scales ($P < .05$). Differences in these groups with respect to sex, age, tumor site, or stage could not be found.

**Conclusion:** Given that only patients with locally (anatomic or functional) inoperable stage IV disease were treated, the results are promising, underlining the feasibility of the RADPLAT protocol.


Head and neck cancer accounts for 7% of all malignancies in the Netherlands.1 Annually, around 2400 new patients are seen and approximately 600 of them present with advanced stage IV disease. Head and neck cancer is mainly treated with surgery and/or radiotherapy. For the advanced cases, surgery is the mainstay of treatment, often combined with postoperative radiotherapy. However, surgery, often resulting in considerable anatomic changes, has a major impact on the physical and psychosocial functioning of the patients. Despite all recent advances in reconstructive surgery, patients often are negative about resulting disfigurement and report problems with speaking, eating, and social interactions, and feelings of anxiety and depression.2,3 These problems are enhanced by the moderate to poor prognosis of advanced head and neck cancer, often not exceeding a 5-year survival rate of approximately 25%.4 Locoregional cure rates are somewhat better, but a significant proportion of patients will die within 2 years of the onset of their disease because of the development of distant metastases or second primary malignancies.5

The increasing awareness of the functional and psychosocial dysfunction as a result of the often necessary, extensive surgical procedures stimulated the quest for other, less debilitating therapeutic strategies for patients with advanced head and neck cancer. This has led to the development of nonsurgical, organ-preservation approaches, mainly combining chemotherapy and radiotherapy. Until recently, induction and/or (neo)adjuvant chemotherapeutic regimens were applied, but these have not resulted in an improved survival rate.6 There are some indications,
PATIENTS AND METHODS

Fifty consecutive patients diagnosed as having local stage IV head and neck cancer, enrolled in the RADPLAT protocol during the first 1 1/2 years, participated in this QOL study. The study protocol was approved by the medical ethical committee, and written informed consent was obtained from patients before they entered the study.

Patient characteristics, including sites and stages, are shown in Table 1. Staging was accomplished according to the International Union Against Cancer (Union Internationale Contre le Cancer) staging system of 1997. Most patients had extensive T4 disease (n=43), whereas 7 patients had T3 disease involving the base of tongue, in whom surgical resection would have required total glossectomy or glossectomy (considered functionally inoperable because of the devastating end result with respect to swallowing and speech). There were 37 men and 13 women with a mean age of 54 years (range, 41-70 years) and a follow-up of 1 year after initiating treatment. All patients had a history of excessive smoking and (social) alcohol consumption. Only 1 patient indicated that he had quit smoking 13 years before the cancer treatment. During the 1-year follow-up, 16 patients died of their disease or intercurrent (14 and 2 patients, respectively), 5 patients underwent salvage surgery, 2 patients could not be reached (returned to the Netherlands Antilles), and 1 patient refused categorically to be interviewed at the 6- and 12-month assessment points. For subgroup analysis, patients were divided into 2 groups: the “failure” group and the “1-year QOL” group. The patients who died within the first year or were treated for recurrent or residual disease were combined into the failure group. The 26 patients who completed the questionnaire at 12 months of follow-up were combined into the 1-year QOL group. The data for the remaining 3 patients (who were unavailable for follow-up) were used in the analysis, when available, but were excluded in the failure and 1-year QOL subgroup analysis.

In this feasibility study, the protocol of Robbins et al12 was followed. The treatment consists of cisplatin in a dose of 150 mg/m2 administered intra-arterially, with sodium thiosulfate given concurrently, first as an intravenous bolus injection and then continuously as an intravenous infusion, on days 2, 9, 16, and 23. The radiotherapy is given concomitantly in 35 daily fractions of 200 rad (2 Gy) to a total dose of 7000 rad in 7 weeks. Also, the QOL questionnaires incorporated in the aforementioned protocol were applied, to allow better comparison with the results obtained in previous reported studies. Therefore, the Dutch-Flemish translation of the Functional Assessment of Cancer Therapy–Head and Neck (FACT-H&N) and the University of Washington (UW) questionnaire were used. The interviews took place before treatment and at 3, 6, and 12 months after the onset of the treatment. The FACT-H&N questionnaire consists of 28 general and 11 head and neck–specific questions. Items, rated on a 0-to-4 point Likert scale, are combined to describe patient QOL in 6 subscales: physical well-being, social and family well-being, relationship with doctor, emotional well-being, functional well-being, and head and neck–specific symptoms. Higher scores on the various subscales represent a better QOL. To obtain additional, more detailed information, the UW QOL questionnaire was used, consisting of the following categories: pain, disfigurement, activity, recreation, employment, eating (chewing and swallowing), saliva (amount and texture), taste, and speech. All items are rated on a 5-point scale.

For statistical analysis, the FACT-H&N items were combined into a more limited set of multiple-item scales, according to Likert’s method of summated ratings. The reliability of the scales was assessed with Cronbach α. Differences over time within groups were tested with t tests for paired observations, and the 2-sample t test was used to compare differences between groups. The general linear models procedure was applied for repeated measures. Correlations were assessed by Pearson correlation coefficient. A 2-tailed P<.05 was considered statistically significant.

RESULTS

Both the FACT-H&N and UW scales have been used for the first time in our institute. They are self-administered questionnaires. However, if the choice of receiving assis-

Table 1. Patient Characteristics (N = 50)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54</td>
</tr>
<tr>
<td>Mean</td>
<td>54</td>
</tr>
<tr>
<td>Range</td>
<td>41-70</td>
</tr>
<tr>
<td>Sex, No.</td>
<td>Male 37</td>
</tr>
<tr>
<td>Female 13</td>
<td></td>
</tr>
<tr>
<td>T stage, No.</td>
<td>T3 7</td>
</tr>
<tr>
<td>T4 43</td>
<td></td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>12</td>
</tr>
<tr>
<td>Tumor site, No.</td>
<td>Tonsil/lateral oropharynx 14</td>
</tr>
<tr>
<td>Base of tongue</td>
<td>9</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>4</td>
</tr>
<tr>
<td>Tongue</td>
<td>5</td>
</tr>
<tr>
<td>Retromolar trigone/alveolar process</td>
<td>3</td>
</tr>
<tr>
<td>Transglottic or supraglottic larynx/vallecula</td>
<td>6</td>
</tr>
<tr>
<td>Piniform sinus/hypopharynx</td>
<td>8</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1 contains patient characteristics (N = 50). The data are presented as the number of patients in each category.
tance vs self-completion was left to the patient, approxi-
mately three fourths of them asked for some help in com-
pleting the questionnaires (reading and marking items per
the patients’ responses).

In applying the FACT-H&N scale, it appeared that
the translation into Dutch-Flemish was not always opti-
mal (version October 9, 1996). For example, in items
1 and 3 of the physical well-being subscale, a negation
has been used in the sentence, making it very confusing
for the patient to answer. Furthermore, questions about
losing hope and worrying about dying (items 22 and 24
of the emotional well-being subscale) were rather dis-
turbing for the patients, especially in case of recurrence
or metastases. Since many patients used a tube feeding
at some time during and/or after their treatment, several
questions on the head and neck subscale had to be skipped
at that time.

A common problem with the UW questionnaire con-
cerned the item on the amount of saliva. Especially im-
mediately before and after treatment, many patients had
complaints of too much rather than too little saliva. This
answer could not be entered into the 5-point scale of this
item. Also, the item assessing voice quality was not quite
suitable for our patient population. Patients who have
had this nonsurgical treatment do not have problems with
the pronunciation of certain words, but their voice can
be hoarse or lacking in volume.

Despite these minor shortcomings, the reliability
(Cronbach α), assessing the internal consistency of the
Likert scales of the FACT-H&N questionnaire, was ac-
ceptable. In Table 2 the coefficient α is shown at baseline
(N = 50), at 6 months (n = 37), and at 12 months
(n = 26) after the start of treatment. In most scales the co-
efficient α was between 0.68 and 0.90. For the social well-
being subscale, only items 9 through 13 were used; item
14 was excluded, since many patients did not answer that
question if they did not have a partner. The reliability of
the head and neck scale was assessed across 9 items (ex-
clusion of items 42, smoking, and 43, drinking of alcohol).

Table 3 shows the results of the FACT-H&N sub-
scales for the 26 patients in the 1-year QOL group. Three
measuring points are included: pretreatment (baseline)
and 3 months (6 weeks after finishing treatment) and 12
months after onset of the treatment. There was a slight
decline at the 3-month interval and some improvement
after 12 months (higher scores represent a better QOL).
For the functional well-being subscale and head and
neck subscale, these improvements are statistically sig-
nificant (P<.001).

### SPECIFIC PHYSICAL, FUNCTIONAL,
AND PSYCHOSOCIAL RESULTS

To provide more insight information, some functional (head
and neck–related) items, mainly based on the outcome of
the UW questionnaire (n = 26), will be shown in detail. Some
expected problems, such as nausea, only sporadically oc-
curred. Six weeks after treatment, only 3 patients (12%)
were still troubled with nausea, and after 12 months no feel-
ings of nausea were reported. Complaints about pain 3 and
12 months after onset of treatment were as follows: at 3
months, 12 patients (46%) did not experience feelings of
pain, 12 patients (46%) needed regular (nonnarcotic) medi-
cation, and 2 patients (8%) still had severe pain that had
to be controlled by narcotics. At 12 months, 21 patients
(81%) did not experience any pain, while 5 patients (19%)
required regular (nonnarcotic) medication.

After 12 months, only 1 patient (female) reported
that she was troubled by her appearance; she had lost a
lot of weight and her face had become very thin and rather
wrinkled. Eleven patients (42%) noted no changes and
14 patients (54%) noted a minor change in appearance.

At the end of the observation period (12 months),
5 patients (19%) still needed tube feeding, but 3 of them
could combine this with drinking liquids. As shown in
Table 4, 16 patients (62%) had little or no problems
with mastication, while 10 patients (38%) had moder-
ate to very severe problems. Swallowing problems were

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**Table 2. Reliability (Cronbach α) of the FACT-H&N Subscales***

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Baseline (N = 50)</th>
<th>6 mo (n = 37)</th>
<th>12 mo (n = 26)</th>
<th>No. of Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>0.52</td>
<td>0.65</td>
<td>0.68</td>
<td>7</td>
</tr>
<tr>
<td>Social</td>
<td>0.68</td>
<td>0.68</td>
<td>0.73</td>
<td>5</td>
</tr>
<tr>
<td>Relationship with doctor</td>
<td>0.86</td>
<td>0.77</td>
<td>0.73</td>
<td>2</td>
</tr>
<tr>
<td>Emotional</td>
<td>0.57</td>
<td>0.76</td>
<td>0.79</td>
<td>5</td>
</tr>
<tr>
<td>Functional</td>
<td>0.74</td>
<td>0.87</td>
<td>0.90</td>
<td>7</td>
</tr>
<tr>
<td>Head and neck</td>
<td>0.73</td>
<td>0.78</td>
<td>0.82</td>
<td>9</td>
</tr>
</tbody>
</table>

*FACT-H&N indicates Functional Assessment of Cancer Therapy–Head and Neck.

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**Table 3. Results of the FACT-H&N Subscales (n = 26)**

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Baseline</th>
<th>3 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>22.9 (3.8)</td>
<td>20.8 (3.4)</td>
<td>21.9 (4.2)</td>
</tr>
<tr>
<td>Social</td>
<td>17.2 (3.0)</td>
<td>16.0 (4.3)</td>
<td>17.2 (2.6)</td>
</tr>
<tr>
<td>Relationship with doctor</td>
<td>7.1 (2.8)</td>
<td>7.0 (1.9)</td>
<td>6.9 (1.1)</td>
</tr>
<tr>
<td>Emotional</td>
<td>16.2 (2.8)</td>
<td>17.1 (3.3)</td>
<td>16.8 (3.7)</td>
</tr>
<tr>
<td>Functional</td>
<td>15.2 (5.7)</td>
<td>15.1 (4.4)</td>
<td>19.6 (6.4)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>23.3 (6.1)</td>
<td>20.8 (6.4)</td>
<td>25.7 (6.5)</td>
</tr>
</tbody>
</table>

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present in 7 patients (27%). Seventeen patients (65%) complained about the decrease in the amount of saliva, while 14 patients (54%) reported that the saliva was “thicker than normal” or “dried in their mouth and/or on their lips.” No statistically significant correlations were found between the amount of saliva and mastication or swallowing. The taste of food returned to normal in 18 patients (69%), while for 6 patients (31%) some of the food still did not taste as it used to.

Concerning the voice quality and strength, based on item 38 (FACT-H&N), 16 patients (61%) reported that their voice was normal, 7 patients (27%) reported somewhat normal, and in 3 patients (12%) the voice was still far from what it used to be.

Twelve months after onset of treatment, 14 patients (54%) smoked again or still, while 18 patients (69%) drank alcohol again or still (Table 5). There was a clear increase in smoking and drinking habits over time, since at 3 months only 9 patients (35%) still smoked and only 7 (27%) still consumed alcohol.

Of the 18 patients (69%) who had a job before their illness, 5 started to work again after 6 months, while at 12 months a total of 10 patients were back at their jobs. Thus, slightly more than half of the potential workers (10/18) returned to their professional lives.

**GROUP COMPARISON**

The mean scores on the FACT-H&N questionnaire of the 1-year QOL group (n = 26) and the failure group (n = 21) are shown in Table 6. The failure population scored lower on all subscales. These differences, before treatment and at 6 months after onset of treatment, assessed by a t test for group comparisons, were statistically significant (P < .001 and P < .05, respectively) for the physical (before treatment), emotional (6 months after treatment), functional (before and 6 months after treatment), and the specific head and neck symptom subscales (before and 6 months after treatment).

Differences in baseline means (Tables 3 and 6) of the 1-year QOL group are explained by missing data in the different subscales at the 12-month interview. If some items, for example, of the head and neck subscale were not applicable for patients who still had tube feeding at that time, the patient would be eliminated for the general linear models procedure for repeated measures, resulting in a group number of 25 or 24 instead of 26. The baseline means in Table 6 are from all 26 patients in the 1-year QOL group.

Statistical analysis of outcome by site was precluded because of the small numbers of patients with different disease sites.

The aim of this feasibility study was to assess the QOL and functional outcome of patients with locally (anatomic or functional) inoperable stage IV head and neck carcinoma during the first year after an intra-arterial cisplatin-based chemoradiotherapy protocol (RADPLAT).12

As expected, the means of the different subscales showed a treatment-related decline and an improvement in the period from 3 months to 1 year of follow-up for the 1-year QOL group. The domains most affected by tumor and treatment, such as functional well-being and head and neck–related symptoms, improved significantly over time, exceeding pretreatment values. However, patients with advanced head and neck cancer already begin their treatment with a compromised QOL.13 The other subscales showed only minor changes during the follow-up period, suggesting that patients’ feelings of emotional and social well-being were relatively independent of the treatment and functional limitations, as was also demonstrated by List et al.21

Although the FACT-H&N questionnaire clearly assesses specific disease- and treatment-related experiences of patients with head and neck cancer,24,25 the addition of the UW questionnaire provided useful detailed information on specific areas such as pain, disfigurement, mastication, swallowing, taste, xerostomia, and work.20 Pain, especially that experienced immediately after treatment, could mostly be treated with nonnarcotic medication. As expected, the problem of treatment-related disfigurement was minor after successful organ preservation treatment: at 12 months, only 1 patient reported being troubled by her appearance. Because of severe weight loss, her face had become rather wrinkled.

Concerning the dysfunction domain, however, problems still exist. With respect to eating problems, most patients regained more or less normal oral feeding possibilities, but 5 patients (19%) at 1-year follow-up still needed tube feeding, 3 of them because of mastication problems and 2 of them because they could hardly swallow. Although formal assessment of dentition was not in-
cluded in this study, personal observations suggest that in some patients the mastication problems were related to their dental situation, as was recently also observed by others.33,27 Optimizing the fit of dentures has to wait until the oral adverse events, such as edema and soreness, subside. Often, patients still were in the middle of their dental rehabilitation program at the end of the first year. Another aspect in the dysfunction domain, ie, the sense of taste, as expected, appeared to be severely affected immediately after treatment. Many patients reported that their food tasted like wet cardboard. During the follow-up period, in most patients the normal sense of taste returned. Only 6 patients mentioned that some specific types of food did not yet taste like they used to (eg, spicy food).

The most frequent complaint concerned xerostomia, which is one of the most commonly encountered consequences of radiotherapy.23,37,28 All patients noted a decrease in the amount of saliva. Also, complaints about the consistency (thicker, more sticky than it used to be) were frequently reported.

With respect to voice, after 12 months the quality and the strength of the voice in 3 patients still was severely compromised. They could hardly make themselves understood. The sites of the tumors in these patients were oropharynx, piriform sinus, and base of tongue, respectively. The voice results after RADPLAT treatments were oropharynx, piriform sinus, and base of tongue, respectively. The voice results after RADPLAT were more favorable than those after surgical treatment. Deleyiannis et al29 compared surgically and nonsurgically treated patients with advanced oropharyngeal cancer. They demonstrated that the speech of 67% of the surgically treated patients deteriorated vs 43% of the nonsurgically treated patients. Also, a previous study assessing consequences of composite resection noted that two thirds of the patients reported reduced intelligibility in face-to-face conversation, mostly because of rhinolalia aperta.7

It is noteworthy that the recovery period after chemoradiation (RADPLAT) is very different for each individual. In our study, of the 18 patients who had a job before treatment, 5 already were at work after 6 months and another 5 at the 12-month assessment interview, while the remaining 8 patients needed more time before they would be able to return to work. These individual differences in time needed to recover are in contrast to what happens after surgery. Pauloski et al28 found that the level of functioning at the 1- and 3-month posthealing evaluations was characteristic of their patients’ status at 1 year after surgery. They found no progression in functioning between 1 and 12 months after surgery.

Although self-reported data on alcohol consumption and tobacco use are seldom reliable, items 42 and 43 of the FACT-H&N questionnaire will probably distinguish between the smokers and nonsmokers and between the alcohol consumers and nonconsumers. The results show that 14 of the 25 patients smoked again (1 patient had quit smoking 13 years before the treatment), while 18 of the 26 drank alcohol again at 12 months. Most of them added that they drank and smoked a lot less than they used to. According to the patients, alcohol was consumed only during weekends and birthday parties. These disappointing data show that, despite the information about the influence of continued smoking (often in combination with alcohol) on the sequelae of treatment, prognosis, and development of secondary malignancies, many patients continue to smoke and drink.28,30

Statistically significant pretreatment differences were found between the 26 patients who were still alive at 12 months (the 1-year QOL group) and those who died or had to undergo extensive surgery within 12 months (the failure group) on the FACT-H&N physical, functional, and head and neck subscales. This means that already at baseline the patients in the failure group presented with lower pretreatment scores than the 1-year QOL group. This is in contrast to a recent study by List et al,30 who noted no statistically significant pretreatment differences between patients still alive and without disease at 12 months and those who died within 12 months. Further analysis showed that posttreatment scores of the survivors increase, while the scores of the failure group continue to decrease. The decline in those specific subscales (functional well-being and the head and neck subscales) may explain the more prominent feelings of distress (emotional well-being subscale) in the failure group. Patients often start the chemoradiation treatment optimistically, but if during follow-up local recurrence or distant metastases are diagnosed, obviously feelings of emotional well-being decrease.

As expected, the results show a decline on most subscales and specific head and neck symptoms during and shortly after treatment. However, a statistically significant improvement in the functional well-being and the head and neck subscale is noted over time. The recovery period after RADPLAT therapy shows a considerable variability between the individual patients. Ten of them returned to their jobs within 12 months, while others needed more time to recover. Considering the extent of the local disease (most patients having T4 lesions), problems with eating recovered relatively well, with 80% of the patients returning to a more or less normal oral diet. Xerostomia remains a residual complication inherent in the nature of radiotherapy. For 23 patients (88%), the quality and strength of the voice was more or less normal. Further analysis showed already statistically significant differences in pretreatment scores between the 1-year QOL group and the failure group. This concerns physical well-being, functional well-being, and the head and neck subscales. Differences in these groups with respect to sex, age, and tumor site or stage could not be found.

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