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Radiotherapy with carbogen breathing and nicotinamide in head and neck cancer: feasibility and toxicity

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Received 27 July 1995; revision received 25 September 1995; accepted 27 September 1995

Abstract

The feasibility and early toxicity of radiotherapy with carbogen breathing and nicotinamide was tested in 74 head and neck cancer patients. Forty patients with laryngeal and hypopharyngeal tumors were treated with an accelerated schedule combined with carbogen alone (16) or with carbogen and nicotinamide (24). Thirty-four patients with far advanced unresectable tumors of the oral cavity and oropharynx received conventional radiotherapy with carbogen [16] or with carbogen and nicotinamide (18). Some enhancement of skin reaction was observed with nicotinamide but this remained well within limits of tolerance. With the accelerated regimen there was increased severity of mucosal damage expressed as confluent mucositis in 95% of patients which required healing times of 3–4 months in four patients. Eventually restoration of the mucosal lining was complete in all cases. Nausea and vomiting are the most frequent side effects of nicotinamide and were reported by 60% and 36% of the subjects, respectively. In 26% this was reason to discontinue drug intake. Severe renal dysfunction was associated with nicotinamide intake in two patients of this study and in one other patient who presented later. It is our conclusion that radiotherapy combined with carbogen and nicotinamide is a safe treatment with manageable side effects. We recommend not to give nicotinamide concomitantly with nephrotoxic medication or to patients who have impaired renal function. Preliminary tumor control rates are encouraging and clinical testing will be continued.

Keywords: Radiotherapy; Head and neck cancer; Fractionation; Carbogen; Nicotinamide

1. Introduction

It is well recognized that hypoxia is an important factor determining the radiation response of squamous cell carcinomas. In man, the existence of hypoxia and its relationship to the outcome of radiation therapy has been demonstrated in carcinomas of the head and neck and uterine cervix [5,9,18,19]. Randomized clinical trials with hyperbaric oxygen and hypoxic cell radiosensitizers have shown significantly improved local control rates in carcinomas of the head and neck [7,8,21,22]. However, these approaches have not gained general acceptance. The side effects of many radiosensitizers hamper their clinical use although some newer drugs are less toxic.

Delivery of radiation in hyperbaric oxygen is a demanding technique and often hypofractionation has been used, but this is currently not considered optimal because of reduced sparing of late reacting normal tissues.

Two mechanisms underlying tumor hypoxia are recognized. Chronic hypoxia results from the limited diffusion distance of oxygen in tissue [27], whereas acute or transient hypoxia is caused by local fluctuations in tumor blood perfusion [2,3]. Agents that modify tumor microcirculatory function may reduce acute hypoxia. The amide derivative of vitamin B₃, nicotinamide, has recently received attention in this respect [11,16]. It was suggested that nicotinamide could further enhance the sensitizing effect of carbogen as a method to eliminate chronic hypoxia [24]. Polarographic studies have shown that carbogen (95% O₂ + 5% CO₂) breathing can

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increase the oxygen partial pressure and reduce chronic hypoxia in patients with head and neck tumors [20]. Relative to radiation treatment in air without the drug, enhancement ratios in the order of 1.8 have been obtained for treatment with carbogen and nicotinamide in mouse tumors [17].

Another important factor determining the radiation response of tumors is cellular repopulation. There is evidence from clinical studies that patients with head and neck carcinomas may benefit from accelerated fractionated irradiation to counteract repopulation of tumor clonogens which occurs during the course of treatment [1,26]. Results of randomized trials are expected soon.

Rojas et al. proposed the strategy of combining accelerated radiotherapy with carbogen and nicotinamide (ARCON) to overcome both the compensating effect of tumor repopulation and chronic and acute hypoxia [25]. This is a report on the feasibility and toxicity of this approach in patients with carcinomas of the head and neck.

2. Patients and methods

2.1. Design of the study

Two categories of patients were eligible for the study. One category includes patients with laryngeal (stage III–IV) and hypopharyngeal (stage II–IV) tumors receiving primary radiotherapy as larynx conserving treatment. The other category of patients had far advanced unresectable tumors, mostly of the oral cavity and oropharynx and were referred for palliative radiotherapy. It was planned to first treat 15 patients with carbogen alone in each category. After this had been shown to be feasible and without severe direct toxicity, nicotinamide was added. Since experience was previously obtained with an accelerated schedule in laryngeal cancers [13], it was decided to build on this experience and to add carbogen and nicotinamide as second and third steps, respectively. For the oral cavity and oropharyngeal tumors carbogen breathing and nicotinamide were added stepwise to a conventional radiation schedule. The patients with laryngeal and hypopharyngeal tumors were analyzed separately from those with oral cavity and oropharyngeal tumors because normal tissue effects as well as treatment outcome are expected to be different in the two groups.

This work was approved by the local ethical committee.

2.2. Patients

Seventy-four consecutive patients were entered into the study over the period November 1992 until February 1995. Inclusion criteria were: age over 18 years, WHO

performance status of 0–2, no severe heart or lung disease, no severe liver or kidney function disturbances, no severe stridor, no distant metastases, and written informed consent. Another six patients were eligible but refused participation. Thirteen patients were ineligible for the following reasons: poor performance status (9), severe cardiac and pulmonary disease (4), claustrophobia (1), and Rendu-Osler-Weber disease with severe anemia (1). The patients entered in the study had a mean age of 57 years (range 27–82 years). There were 60 men and 14 women. All patients had squamous cell carcinomas except one with a mucoepidermoid carcinoma of the larynx. Three patients had two concurrent primary tumors in the head and neck area. Two other patients had recurrent disease after surgical treatment. Characteristics of the patients, their tumors, and the treatment are shown in Table 1.

2.3. Radiotherapy

The primary tumor and bilateral neck nodes were irradiated through lateral opposed photon beams (4 and 6 MV). The inferior border was generally placed just superior to the arytenoids for oral cavity and oropharyngeal tumors. For tumors of larynx and hypopharynx the inferior border was placed just above the shoulders. After 30–40 Gy, an off-cord reduction was made and the posterior cervical chains were treated with lateral appositional electron beams. The mid- and lower-neck nodes were treated with an anterior photon field. In some cases a posterior field was added to supplement the dose in the posterior midcervical chains. The boost dose was delivered through reduced lateral or oblique opposed portals combined, when necessary, with an electron beam to boost nodal areas overlying the spinal cord or larynx. Conventional radiotherapy was given in fractions of 2 Gy, five times a week. Total dose was 68 Gy for gross disease and 44 Gy for the areas treated electively. Overall treatment time was 46–48 days. With the accelerated schedule, the dose per fraction remained 2 Gy but treatment time was reduced by 10 days by giving two fractions per day during the last one and a half weeks of treatment. Intervals between fractions was at least 6 h.

Sensitization of laryngeal cartilage has been reported after radiotherapy in hyperbaric oxygen [8]. A 10% reduction of total dose in a subsequent study of hyperbaric oxygen reduced the laryngeal complications to a level seen with treatment in air [7]. Since a similar effect might be expected from normobaric carbogen with nicotinamide, the maximal permissible dose to the larynx was reduced from 70 to 64 Gy and, as a consequence, tumor dose for primaries of the larynx and hypopharynx did not exceed this limit. Involved nodes received 68 Gy. Because a decrease in tolerance of the rat spinal cord of ~20% was observed when radiation

Table 1
Number of patients according to treatment and site of primary disease and clinical stage (UICC 1992 staging system)

| | Treatment | | | |
|--|----------------|----------------------|---------------|---------------------|
| | Conv RT + Carb | Conv RT + Carb + Nic | Acc RT + Carb | Acc RT + Carb + Nic |
| No. patients | 16 | 18 | 16 | 24 |
| Mean age (range) | 55 (41–76) | 53 (27–73) | 60 (39–82) | 60 (41–78) |
| Stage | | | | |
| T _x | — | 1 ^b | — | — |
| T ₁ | 2 | — | — | — |
| T ₂ | — | — | 7 | 7 |
| T ₃ | 5 ^a | 8 ^c | 8 | 13 |
| T ₄ | 8 | 9 | 1 | 4 |
| N ₀ | 3 | 3 | 6 | 11 |
| N ₁ | 2 | 4 | 7 | 5 |
| N _{2a} | — | — | — | — |
| N _{2b} | 1 | 5 | 2 | 1 |
| N _{2c} | 8 | 4 | 1 | 7 |
| N ₃ | 1 | 2 | — | — |
| Not classable | 1 | — | — | — |
| Site of primary | | | | |
| Oral cavity | | | | |
| Oral tongue | 1 | 3 | — | — |
| Floor of mouth | — | 5 ^b | — | — |
| Oropharynx | | | | |
| Soft palate | 1 | 1 | — | — |
| Tonsillar fossa | 5 | 5 ^c | — | — |
| Base of tongue | 7 ^a | 3 | — | — |
| Pharyngeal wall | 1 | — | — | — |
| Maxillary sinus | — | 1 | — | — |
| Auditory canal | 1 | — | — | — |
| Larynx | | | | |
| Supraglottic | — | — | 10 | 11 |
| Glottic | — | — | 3 | 5 |
| Hypopharynx | | | | |
| Pyriform sinus | — | — | 2 | 6 |
| Postericoid | — | — | 1 | 2 |
| No. patients receiving chemotherapy | 8 | 8 | — | 2 |

^aOne patient with synchronous second primary of soft palate (T2).

^bOne patient with synchronous second primary of pyriform sinus (T2).

^cOne patient with synchronous second primary of vallecula (T1).

was combined with carbogen and nicotinamide [6], total dose to the spinal cord was not higher than 40 Gy. Dose specification was according to Report 29 of the ICRU [12].

2.4. Carbogen breathing

Scuba-diving equipment was used for carbogen delivery. This system transports the gas from the reservoir to the patient by way of a two-step pressure reduction. The second stage of the breathing regulator is connected to a disposable anesthetic face mask which is incorporated in the immobilizing cast. Details of this breathing system have been described earlier [14]. Carbogen breathing

commenced 4 min before start of irradiation of the macroscopic tumor localizations and was continued throughout the treatment. During the 4-min pre-irradiation breathing time fields were set up and uninvolved supraclavicular nodes were treated. Pre-irradiation breathing time and total breathing time were recorded.

2.5. Nicotinamide

Nicotinamide, dissolved in fruit juice, was administered orally 1.5 h before irradiations. On days when two fractions were given, only one dose of nicotinamide was taken before the first treatment. In-

initially the daily dose was 6 g. After April 1994, when more pharmacokinetic data became available, this was changed to a weight-adjusted dose of 80 mg/kg with a maximum of 6 g.

2.6. Monitoring during treatment

Blood pressure and heart rate were measured on the first 5 treatment days just before and after irradiations. This was discontinued after the first 20 patients because no changes had been observed.

Blood samples were drawn once a week for blood cell counting and hemoglobin concentration measurement. When hemoglobin concentrations fell below 7 mmol/l this was corrected by blood transfusions. Initially, serum liver enzymes, sodium, potassium, urea, and creatinine were determined before and in the last week of the treatment. Later this was also done weekly during the course of irradiation.

Weekly assessment of acute mucosal and skin reactions started in the first week of treatment and continued during treatment and thereafter until the lesions started to heal. Patients were then seen once every 2 or 3 weeks until healing was complete. Reactions of mucosa and skin and dysphagia were scored as shown in Table 2. Since 1987 this scoring system is applied routinely to all patients receiving radiotherapy to the head and neck area in our institute.

2.7. Additional treatment

Eighteen patients received chemotherapy prior to radiation treatment. In most cases this consisted of cis-

platin weekly for one to six courses. One patient was treated with three courses of methotrexate, bleomycin, vinblastine, and cisplatin. All these patients had far advanced unresectable tumors. After radiotherapy two patients underwent neck dissections for residual nodal disease

2.8. Statistics

Fisher's exact probability test was used to test the significance of differences in acute toxicity scores between groups. Average durations of mucosal and skin reactions were compared by the *t*-test.

3. Results

3.1. Carbogen breathing

Measurements of blood pressure and heart rate before and after carbogen breathing were discontinued after no apparent changes were observed in the first 20 patients. Six of the 74 patients were unable to continue carbogen breathing throughout the entire course of irradiation. Two patients underwent a tracheostomy, one because of edema and the other because of tumor progression; the other four patients experienced sensations of suffocation, sometimes accompanied by extreme hyperventilation. Pre-irradiation breathing time was less than 4 min in 1.2% (25/2123) of radiation sessions but never less than 3 min. It was longer than 6 min in 5.8%, usually due to delays in the treatment set up. Total breathing time was more than 15 min 6.7% of times, mostly when complicated techniques were used to limit the dose to the spinal cord.

3.2. Nicotinamide

The most common side effects from nicotinamide were nausea and vomiting, reported, respectively, by 25 (60%) and 15 (36%) of the 42 patients taking the drug. Ten patients were nauseous after the first dose of nicotinamide. Often these complaints were unresponsive to anti-emetics including ondansetron. Eleven patients (26%) discontinued the intake of nicotinamide due to severe nausea and vomiting. One patient was under treatment when adjustments of nicotinamide dose were made from 6 g to individual weight-corrected doses. In this patient nausea disappeared when the dose was reduced from 6 to 4 g (80 mg/kg). Apart from this one patient we observed no differences in side effects between patients taking 6 g and those taking 80 mg/kg. Five patients reported flushing 0.5–2 h after ingestion. One patient showed signs of depression which disappeared within a few days after nicotinamide was discontinued. One patient refused to continue nicotinamide intake because of the bad taste. No serum liver enzyme

Table 2
Scores for mucosal and skin reactions

| Acute reactions | Score |
|--|-------|
| Mucosa | |
| normal | 0 |
| slight redness | 1 |
| severe redness | 2 |
| spotted mucositis | 3 |
| confluent mucositis \leq 50% of irradiated surface | 4 |
| confluent mucositis $>$ 50% of irradiated surface | 5 |
| Dysphagia | |
| no complaints | 0 |
| complaints, no medication | 1 |
| medication needed | 2 |
| liquid feeding | 3 |
| tube feeding | 4 |
| Skin | |
| normal | 0 |
| slight redness | 1 |
| severe redness | 2 |
| dry desquamation | 3 |
| moist desquamation \leq 50% of irradiated surface | 4 |
| moist desquamation $>$ 50% of irradiated surface | 5 |

disturbances related to nicotinamide were observed. Twelve patients had isolated elevation of γ -glutamyl transpeptidase (γ -GT), mostly already before start of treatment, which was ascribed to alcohol abuse.

Two patients developed severe renal dysfunction following nicotinamide administration. Patient 1 received daily doses of 6 g and patient 2 received 5.5 g. Both patients complained of nausea and vomiting and patient 2 also had severe diarrhea. This was reason to discontinue the drug in both patients. Both were admitted to the hospital a few days later with dehydration and renal dysfunction. Patient 1 was known to suffer from type I diabetes mellitus and hypertension and concomitant medication consisted of insulin, lisinopril (angiotensin converting enzyme-ACE-inhibitor), bisoprolol (selective β -blocker), carbasalatcalcium and ondansetron. Patient 2 was on metoclopramide, oxazepam and an antacid. Prior to the start of radiotherapy he received six weekly cycles of cisplatin, 70 mg/m². Maximum recorded serum levels of creatinine were 2290 μ mol/l in patient 1 and 1096 μ mol/l in patient 2. Renal function recovered with rehydration and bicarbonate administration in both patients. In addition, both patients developed

thrombopenia of uncertain etiology. Patient 1 also had moderate and transient elevation of liver enzymes 2 weeks after discontinuation of nicotinamide. She fully recovered and could resume radiotherapy. Patient 2 had an episode of ventricular tachycardia, possibly as a result of electrolyte disturbances. He had a large unresectable tumor and progression of disease already under chemotherapy and it was decided to stop further radiation treatment because of the very poor prognosis.

3.3. Radiotherapy

Three patients did not complete the planned radiation treatment. One patient died from a massive bleeding in the tumor, one patient developed distant metastases during loco-regional treatment and the third patient as mentioned above had rapid tumor progression, renal complications and deterioration of general condition. Total treatment duration exceeded 48 days in four of the 34 patients treated according to the conventional schedule. Reasons were: renal complications (6 days); tracheostomy (1 day); machine breakdown (1 day); holiday, not compensated for (1 day). Of the 40 patients

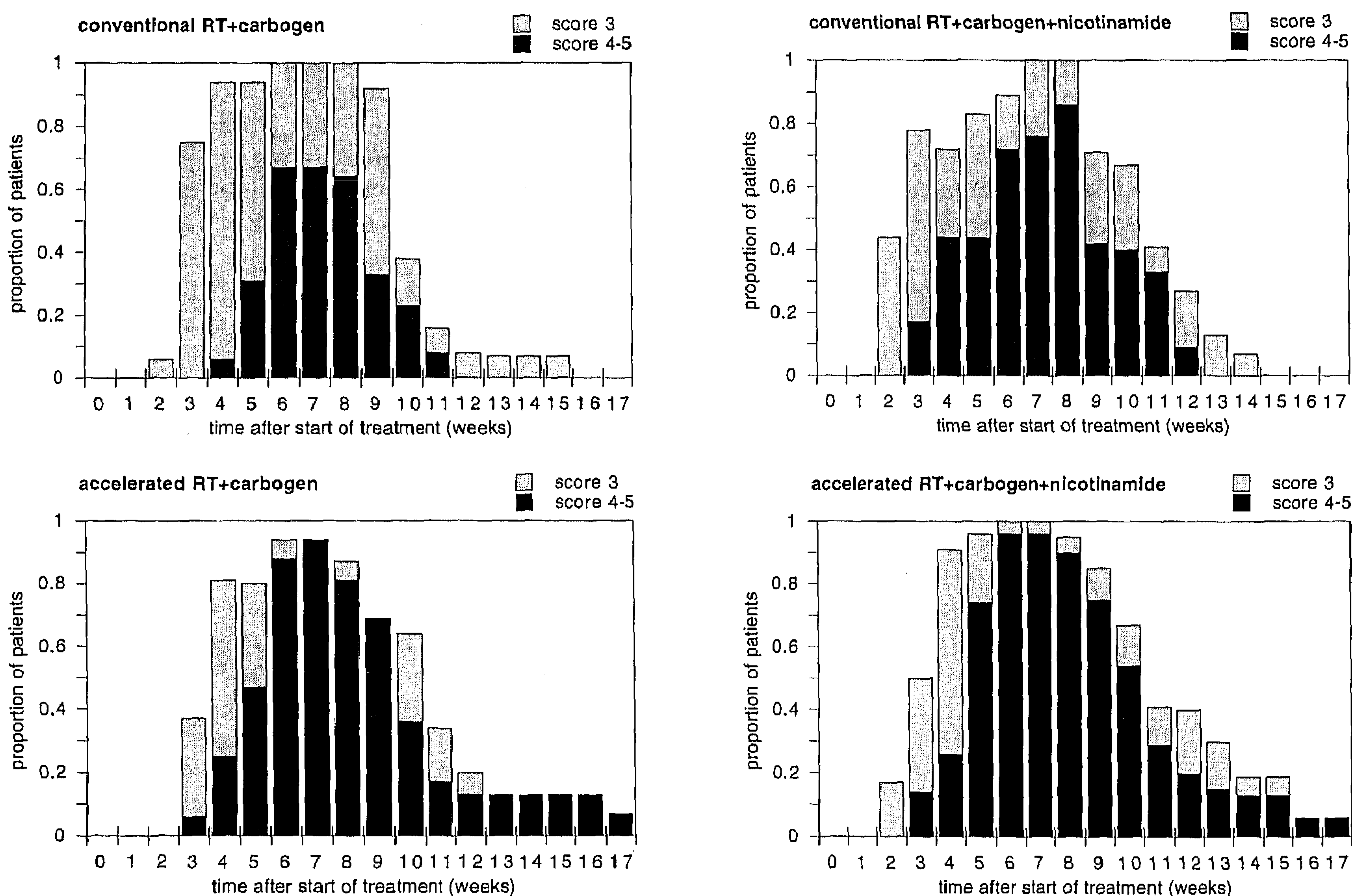


Fig. 1. Scores for mucosal reactions: proportion of patients reaching a certain score versus time after start of radiotherapy (RT).

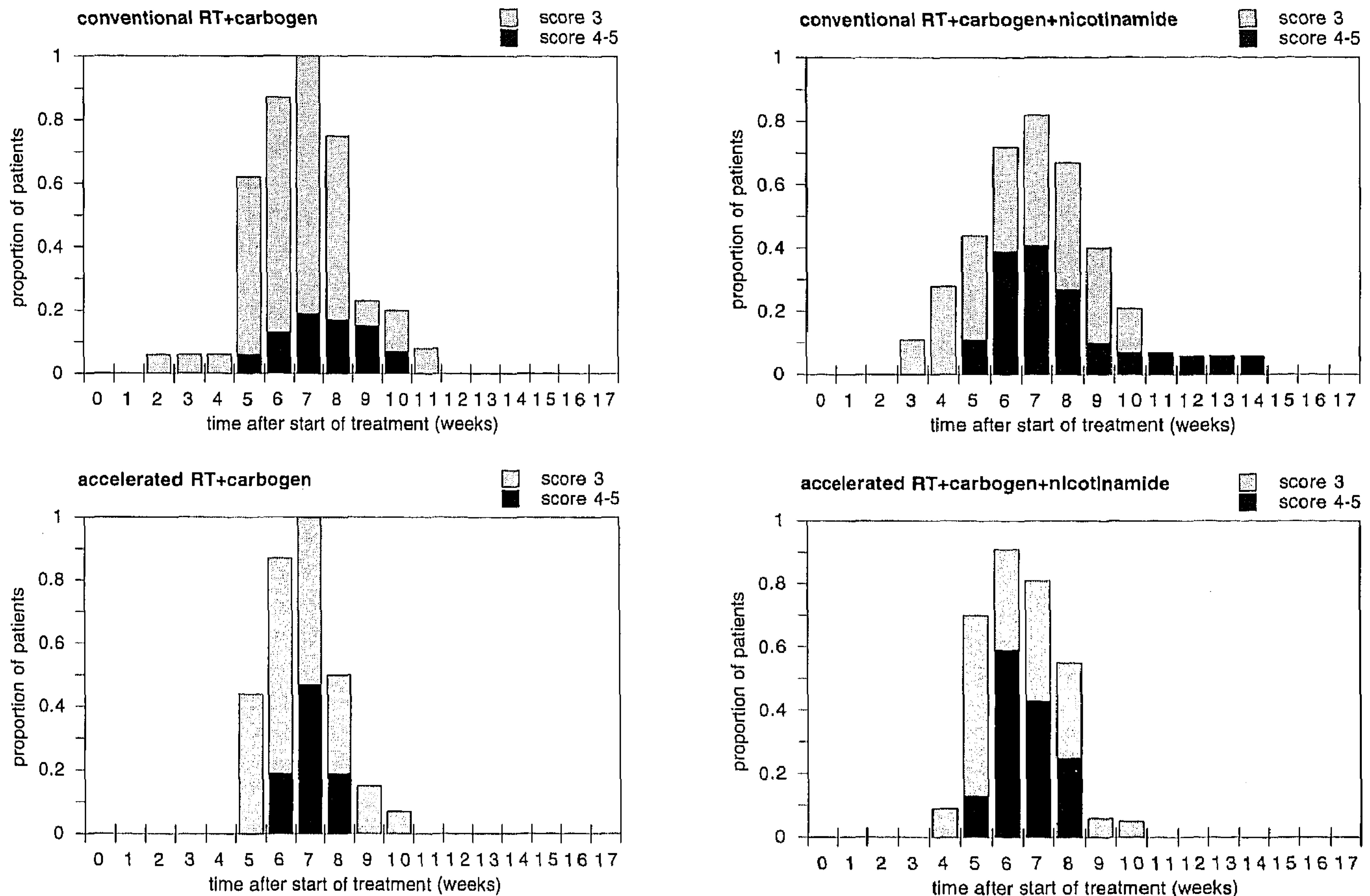


Fig. 2. Scores for skin reactions: proportion of patients reaching a certain score versus time after start of radiotherapy (RT).

treated by the accelerated schedule only one surpassed the maximum allowed treatment time of 38 days with a single day because of a holiday that was not compensated for.

3.4. Early reactions of mucosa and skin

Scores for acute radiation reactions during and after treatment are shown in Figs. 1 and 2. Only the highest scores are shown because scores 1 and 2 have limited clinical significance and are nearly always followed by more severe reactions. For the group of patients treated with conventional radiotherapy and carbogen (C) confluent mucositis occurred in 81% of the cases, and with addition of nicotinamide (N) this was 83%. Average duration was 3.5 (C) and 5.1 (C+N) weeks ($p = 0.08$, t -test). The accelerated schedule caused confluent mucositis in all but two cases (95%) with an average duration of 6.3 (C) and 6.7 (C+N) weeks. Prolonged duration of confluent mucositis, i.e., persisting more than 6 weeks after the end of treatment, was observed in four patients after the accelerated regimen. In all cases healing was complete within 3-4 months after treatment. Tube feeding was needed in 29% of patients

with oral cavity and oropharynx tumors and in 26% of patients with laryngeal and hypopharyngeal tumors with no significant differences between patients receiving carbogen alone and those receiving carbogen and nicotinamide. Objective and functional mucosal reactions were not more severe for patients who received chemotherapy prior to irradiation (data not shown).

Addition of nicotinamide appeared to somewhat increase skin reactions. The conventional schedule with carbogen caused moist desquamation in four of 16 patients (25%) and in 10 of 18 patients (56%) who received also nicotinamide ($p = 0.06$, Fisher's exact test). With the accelerated schedule this was nine of 16 (56%; C) and 15 of 23 (65%; C+N). Generally the skin healed rapidly within 3 weeks except in one case in which it required 7 weeks. This patient was in the conventional schedule with carbogen and nicotinamide.

3.5. Locoregional tumor control

All 39 patients with tumors of larynx and hypopharynx who finished the planned course of irradiation had complete disappearance of locoregional tumor at 6 weeks after the end of treatment. Actuarial

locoregional control at one year was 86%, with 21 patients being in follow-up at least a year after treatment. Thirty-two patients with oral cavity and oropharynx tumors completed treatment, of whom 20 (63%) had complete regression of disease at 6 weeks. The one-year actuarial locoregional control rate for this group was 41%, with 23 patients in follow-up one year or more after treatment.

4. Discussion

Carbogen breathing by the method described previously [14] appears to be feasible and well tolerated, even by patients with large tumors in the upper aerodigestive tract. Only four of 74 patients were unable to cope with the procedure because they experienced sensations of suffocation, in some cases with hyperventilation which is caused by the carbon dioxide component of the gas. Polarographic O_2 measurements in metastatic lymph nodes from head and neck carcinomas showed that breathing time before optimal oxygenation was 4 min or less in 19 of 20 patients [20]. It was also demonstrated that tumor pO_2 starts to decline after 12–18 min of carbogen breathing [4]. Thus, irradiations are best delivered between 4 and 15 min after the start of carbogen breathing when tumor oxygenation is at its peak level. This was accomplished in 92% of our radiation sessions.

Reported side effects of nicotinamide are: nausea, vomiting, flushing, facial erythema, headache, fatigue, cutaneous reactions, and rare events of liver toxicity [29]. Doses of nicotinamide of up to 6 g daily were described as reasonably safe and associated with a low incidence of side effects. In our experience, with doses of 6 g/day or 80 mg/kg/day, nausea and vomiting occurred frequently and necessitated discontinuation of the drug in 26% of patients. Gastrointestinal symptoms were also reported in other clinical pilot studies: three of six patients with head and neck cancer [30], two of six patients with breast cancer [23], and in two of 16 patients with malignant gliomas [28]. The mechanism by which these symptoms are produced is not clear: there may be a systemic effect or topical irritation of the gastrointestinal mucosa. In the latter case, an alternative route of administration might reduce these unpleasant side effects. Severe renal dysfunction was associated with nicotinamide intake in two patients. When this article was being finalized a third patient presented with this complication, also after previous treatment with cisplatin. Thus, two patients received previous (cisplatin) and one concomitant (ACE-inhibitor, carbasalcalcium) nephrotoxic medication. This, in combination with decreased renal flow due to hypovolemia as a result of nicotinamide-induced vomiting and decreased oral fluid intake, may well be the cause of rapidly developing renal failure. Any direct renal toxicity from nicotinamide can,

however, not be excluded. It was shown that the drug inhibits renal clearance of $^{51}CrEDTA$ and ^{125}I -iodohippurate in mice [10]. These effects were dose-related and evident at doses from 400 mg/kg upwards which is considerably higher than the doses clinically applied. Only one previous case of renal toxicity in man has been reported by Zackrisson et al. [30]. This patient received two daily doses of 6 and 3 g. He had a known cardiomyopathy and was on treatment with an ACE-inhibitor as was one of our patients. The patient had nausea and vomiting and developed hypotension with elevation of serum creatinine and liver enzymes. Plasma concentrations of nicotinamide and its metabolites suggested that renal elimination was impaired. Possibly in patients with compromised renal function (nephrotoxic medication, hypovolemia) nicotinamide accumulates in the plasma to a level at which it can aggravate renal dysfunction and may lead to severe renal failure.

Unlike our experience with glioma patients [28], we did not observe nicotinamide-related hepatic toxicity in this category of head and neck cancer patients. One of the patients with renal complications had moderate elevation of liver enzymes but this was unlikely to be related to nicotinamide intake because it started 2 weeks after discontinuation of the drug. Apparently it was the combination with anti-epileptics and steroids that induced liver toxicity in the glioma patients.

Nowadays with the availability of megavoltage equipment the incidence of severe skin reactions is low. We previously reported an 8% rate of moist desquamation for conventional radiotherapy with total doses of 68–70 Gy [13]. In this study we observed rates of 25% (C) and 56% (C+N). This increased skin reaction is not unexpected as enhancement ratios of 1.3–1.5 were estimated for rodent skin [17]. With the accelerated schedule alone 50% of patients develop moist desquamation [13]. When carbogen and nicotinamide are added there is only a small further increase to 56% (C) and 65% (C+N) which is not statistically significant. Apart from one case, skin lesions healed rapidly. The early reacting tissue of greater clinical significance is the mucosal membrane. With the conventional schedule, 81% (C) and 83% (C+N) of patients in this study developed confluent mucositis of the oral cavity and oropharynx. This corresponds to the 78% rate that we observed when these areas were treated with radiotherapy alone [15]. Acceleration of treatment causes confluent mucositis in up to 90% of patients with laryngeal cancer, with complete healing within 6 weeks after completion of treatment in all cases [13]. In this study confluent mucositis occurred in 95% of patients (C and C+N). However, four patients had healing times of up to 4 months. A possible increase of severity of mucosal damage by addition of carbogen and nicotinamide may well be expressed as delayed recovery. We believe that the acute radiation toxicity as observed with the current regimen is acceptable but we do not ad-

vocate further intensification of treatment as this might lead to non-healing lesions and consequential late effects.

In conclusion, it is our opinion that radiotherapy combined with carbogen and nicotinamide is a safe treatment with manageable side effects. No expensive additional equipment is needed and it requires hardly any extra machine time. Certain precautions should be taken, however, especially with regard to nicotinamide administration. We recommend that nicotinamide should not be given to patients presenting with elevated serum creatinine levels and it should not be given concomitantly with nephrotoxic medication. During treatment, renal function should be monitored at least once a week and twice weekly in patients at risk (e.g., those who were treated previously with cisplatin). Adequate oral intake is demanded. When serum creatinine rises above normal levels, nicotinamide should be discontinued immediately and proper hydration must be secured, if necessary by intravenous infusion.

Possibly, side effects of nicotinamide can be limited when individual dose adjustments are made or when an alternative route of administration is used. Currently we are monitoring nicotinamide plasma levels in our patients to assess whether proper levels are obtained when treatment is given on a day to day routine basis and also to investigate if these are related to the observed side effects.

Preliminary tumor control rates are promising and the approach offers potentials for larynx preservation. In the category of far advanced tumors proposed for palliative treatment, complete regressions were achieved and sustained in a significant proportion of the patients. We expect to increase the effectiveness of the treatment for this particular category with introduction of the accelerated schedule. Our experience with ARCON so far is encouraging and we will proceed with further clinical testing.

Acknowledgements

The authors would like to thank J. Liefers for excellent assistance with patient care and data management and J.F.M. Wetzels, Department of Medicine, Division of Nephrology, for advice.

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