The Danish Head and Neck Cancer Study Group

DAHANCA
Protocol 6-91

Radiotherapy of squamous cell carcinoma in glottic larynx

A randomized multicentre study of 5 versus 6 radiation treatments per week

Activated January 1992
CONTENT

I. BACKGROUND
   Purpose
   Overview of trial

II. BEFORE TREATMENT
   Patient selection
   Pre-treatment examination
   Inclusion and randomisation of patients

III. TREATMENT
     Radiotherapy
     Fractionation
     Evaluation of treatment response

IV. AFTER TREATMENT
    Patient follow-up
    Treatment of residual tumour and recurrence
    Registration and communication
    Statistics
       Analysis
       Publications
       Ethics

V. REFERENCES

Appendix 1: Written patient information
1. BACKGROUND

Squamous cell carcinoma in the head and neck region is becoming a still more frequent disease. In Denmark, an annual total of some 600 cases of cancer in larynx, pharynx, and oral cavity are registered. Excessive use of tobacco and alcohol are among the causative factors for this. Characteristically squamous cell carcinoma in the head and neck is a loco-regional disease, i.e. it is found in T- and N-position, whereas distant metastases are rarely seen at time of diagnosis (1). Radiotherapy and surgery are thus the treatment of choice for the loco-regional disease. In Denmark, there is a long-standing tradition for primary radiotherapy of all larynx and pharynx carcinomas and a considerable number of tumours in the oral cavity. The radiation treatment is scheduled so as to induce optimal tumour control and cause minimal normal tissue complications, also when it comes to surgical treatment of recurrence. The treatment is coordinated on a national level by the Danish Head and Neck Cancer Study group (DAHANCA). So far, DAHANCA has established two national treatment protocols utilizing hypoxic radiosensitizers which have resulted in significantly improved treatment results in patients suffering from pharyngeal and supraglottic laryngeal carcinoma (2,3,4,5).

There are 3 different biological factors of importance for the outcome of a radiation treatment (6,7,8).

Firstly, there is the intrinsic cellular radiation sensitivity. This factor varies very much among head and neck cancer patients (9); but since it is a genetically dependent variation it cannot be modified in others ways but by allocation to various forms of therapy.

Secondly, the tumour environment and especially the presence of oxygen (10) play a role. Tumour cells having insufficient oxygen supply do demonstrate a significant radiation resistance compared with well oxygenated cells. Head and neck cancer is often characterized by areas of no or low oxygen tension which may cause the tumours to be resistant to radiation treatment (10). A treatment strategy in potentially hypoxic tumours has been the use of hypoxic radiosensitizers. These were the basis for the two previous DAHANCA protocols. The first (DAHANCA2) evaluated the radiation response of the hypoxic radiosensitizer Misonidazole, which gave a significantly improved effect in carcinomas of pharynx and supraglottic larynx (2,3), but also an unacceptable neurotoxicity. It was, however, not possible in that study to detect any effect on glottic tumours, and it was concluded that hypoxic radiosensitizers were not indicated in this type of tumours (2,3,5).

The third parameter is associated with the proliferation of tumour cells under treatment. It has been clinically and biologically well documented that a prolonged total treatment time may reduce the chance of tumour control (10,11). This is for instance demonstrated in a Danish study comparing conventional treatment with the so-called split-course therapy (13). Furthermore a number of clinical studies have shown that a reduction in the total treatment time apparently results in improved tumour control (15,16,17). A shorter treatment time may for instance become feasible by applying a higher dose per fraction, but this will result in a disproportionate increase in the incidence of late complications
A shorter treatment time is thus possible only if the weekly number of radiation fractions be increased without increasing the individual fraction size. This is the principle of hyperfractionation giving several fractions per day. Experience has so far been gained from three treatment schedules (15). Either a continuous, very short treatment regimen (CHART) giving 36 fractions in 12 days (including Saturday-Sunday) 3 times a day with an interval of 6 hours (16,21). Or a schedule based on 2 weeks' treatment giving 2 fractions per day, followed by a 2 week break (due to fierce acute reaction) followed by one week of treatment (accelerated split-course) (15,17). Despite the incorporation of a break, the total treatment time is reduced from approximately 7 weeks to 5 weeks. Because of fierce acute reactions of the oral mucosa occurring during the third week of treatment, it is not possible to carry out a continuous treatment schedule. In case of continuous treatment this reaction would demand discontinuation of the treatment, but if the treatment be voluntarily discontinued immediately prior to radiation (i.e. after 2 weeks), the mucosa is stimulated to regenerate and thus allowing a sooner continuation of the treatment than would have been possible if waiting for a full outbreak of the reaction. The ultra-short 12-day regimen is based on applicaton of the full treatment before the mucosa reaction sets in. This reaction will then markedly appear later, but not until the treatment is accomplished. For the time being, this treatment schedule is hardly feasible in Danish hospitals from a practical and economical point of view. Multiple daily fractions necessitate a sufficient interval between the two treatments, which in reality means more than 6 hours to allow repair of radiation-induced normal tissue damage. The third treatment procedure utilizes concomitant boost (15), where the last part of the treatment (boost) is given to a reduced field concomitantly with the last part of the treatment (i.e. 2 fractions per day). This means, that the last 7-10 days of treatment apply 2 fractions per day, giving one fraction to a smaller field to the effect that the total treatment time is reduced. In the last part of such treatment strategy the patients will experience a very fierce reaction of the mucosa. Up till now the evaluation of a regimen using reduced local treatment time has primarily been made on non-randomized, comparative studies where the basic regimen has been "American" (i.e. a dose of 1.8 Gy per fraction as opposed to 2 Gy (European standard)). The American regimen results in a smaller total dose per week as well as a total treatment time one week longer. A comparison with such a relatively weak regimen will thus tend to unfairly misrepresent new accelerated regimens.

Randomized studies of accelerated fractionations are currently undertaken. The MRC examines CHART vs conventional radiotherapy. Within the EORTC a randomized trial is carried out on conventional radiotherapy (70 Gy / 35 fractions / 7 weeks) vs 72 Gy / 45 fractions / 32 days given as accelerated split-course (EORTC 22851). Finally, the RTOG 90-03 compares accelerated split-course with concomitant boost. Within Scandinavia a randomized study of advanced glottic cancer is prepared in which conventional fractionation will be compared with accelerated split-course. The anticipated biological value of this accelerated split-course therapy in squamous cell carcinoma is similar to that of the accelerated treatment in the present protocol, and the aim is to make the two studies directly comparable by introduction of uniform registration and follow-up as well as an identical conventional treatment arm (see table).
### TREATMENT STRATEGIES IN HEAD AND NECK CANCER

<table>
<thead>
<tr>
<th></th>
<th>Dose (Gy)</th>
<th>Number fx</th>
<th>Time (d)</th>
<th>TCP (T-position)</th>
<th>Biol.D (Gy) **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>66.6</td>
<td>37</td>
<td>51</td>
<td>57%</td>
<td>63-64</td>
</tr>
<tr>
<td>Europe I</td>
<td>60.0</td>
<td>30</td>
<td>42</td>
<td>58%</td>
<td>60</td>
</tr>
<tr>
<td>Europe II</td>
<td>66.0</td>
<td>33</td>
<td>45</td>
<td>63%</td>
<td>66</td>
</tr>
<tr>
<td>(DAHANCA 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Split-course</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAHANCA 2</td>
<td>68.0</td>
<td>34</td>
<td>67</td>
<td>43%</td>
<td>68</td>
</tr>
<tr>
<td><strong>Accelerated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.C. Wang</td>
<td>64.0</td>
<td>40</td>
<td>40</td>
<td>62%</td>
<td>57-60</td>
</tr>
<tr>
<td>CHART</td>
<td>50.4</td>
<td>36</td>
<td>12</td>
<td>69%</td>
<td>42-45</td>
</tr>
<tr>
<td>Conc. boost</td>
<td>69.0</td>
<td>38</td>
<td>40</td>
<td>70%</td>
<td>65-67</td>
</tr>
<tr>
<td>EORTC 22851</td>
<td>72.0</td>
<td>45</td>
<td>32</td>
<td>77%</td>
<td>64-67</td>
</tr>
<tr>
<td>SSHNO®</td>
<td>64.6</td>
<td>38</td>
<td>33</td>
<td>70%</td>
<td>60-61</td>
</tr>
<tr>
<td>DAHANCA 7</td>
<td>66.0</td>
<td>33</td>
<td>38</td>
<td>70%</td>
<td>66</td>
</tr>
<tr>
<td><strong>Hyperfract.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 22791</td>
<td>80.5</td>
<td>70</td>
<td>47</td>
<td>73%</td>
<td>62-69</td>
</tr>
</tbody>
</table>

*Male patient, 17.3 ccm poorly diff. squamous cell carcinoma, 8.8 mmol/l HGB.
**Equiv. dose in 2 Gy/fx assuming α/β = 1.8-4.0 Gy, respectively.
*Scandinavian Society for Head and Neck Oncology

The table gives an overview of the various treatment strategies used with the intend to reduce the total treatment time. Total dose, number of fractions and total treatment time are indicated as well as expected tumour control probability (T-position) (TCP) for a patient with oropharyngeal squamous cell carcinoma. Furthermore, the biological dose is indicated assuming an α/β of 1.8 Gy and 4.0 Gy, respectively. These values give the estimated probability for the development of late complications, taking the dose-per-fraction into consideration compared with the established dose-per-fraction dependence for the development of late complications. A low value of the biological dose indicates, that the risk of late complications is relatively small. Data are based on calculations as indicated by Bentzen et al. (12).
Repopulation must be expected to be an important factor, and a reduced treatment time must therefore be considered to be of importance for an optimal treatment result, provided the same total dose or number of fractions be given. On the other hand, such a treatment regimen is characterized by severe acute radiation complications, and it would not be acceptable to introduce it without prior documentation in a controlled clinical trial. Based on a well-defined patient population having oropharyngeal squamous cell carcinoma (12), an assessment of the various accelerated treatment regimens documented a high tumour control probability and an acceptable level of complications, when the 5 weekly fractions of 2 Gy were increased to 6 weekly fractions. This can be done by reintroducing treatment on Saturdays, or by giving an extra fraction on another of the normal treatment days (providing at least a 6 hour interval between fractions). Such treatment schedule will allow a treatment of 66 Gy in 33 fractions to be carried out within a total treatment time which is 8 days shorter than that of the conventional schedule. By an expected repopulation corresponding to 0.5 Gy/day, this will in principle yield a treatment regimen which is approx. 4 Gy “higher” than that formerly used, corresponding to an expected treatment benefit of 7%-15%, depending on the heterogeneity of the patient population (18).

PURPOSE
The purpose of the present study is to improve the radiation treatment given to patients with glottic laryngeal carcinoma, provided they are candidates for primary radiotherapy. The protocol seeks to establish the importance of 5 vs. 6 weekly radiotherapy fractions of 2 Gy given to the same total dose.

The protocol intends to exclude a minimum of patients, to get a true impression of the suitability of such therapy in an approached unselected patient population.

The present protocol constitutes together with the DAHANCA 7-91 protocol, which covers supraglottic laryngeal, pharyngeal and oral cavity tumours a joint study with the main purpose of evaluating the importance of 5 versus 6 fractions per week. In principle, the difference in the two protocols lies in the fact that the present DAHANCA 6-91 protocol deals only with the fractionation effect, whereas the DAHANCA 7-91 also includes treatment with the hypoxic radiosensitizer Nimorazole given to all patients. As mentioned before, there is no indications for giving this drug to patients with glottic carcinomas.
OVERVIEW OF STUDY

A stratified, balanced, and randomized study (phase III) of patients with squamous cell carcinoma in glottic larynx, with the following purpose:
1) to examine whether the total treatment time expressed by 5 or 6 radiotherapy fractions of 2 Gy per week has an influence on:
   a) loco-regional tumour control
   b) incidence of distant metastases
   c) survival (crude, corrected)

2) to estimate to which extent the total radiation treatment time influences early and late complications after radiotherapy.

The study randomizes to 5 or 6 fractions per week and the stratification is based on the following parameters:
- sex
- tumour size (T1-T2 vs T3-T4)
- institution

Other prognostic factors will be analyzed retrospectively.

Patients fulfilling the inclusion criteria will be allocated to one of two fractionation schedules by randomization:

<table>
<thead>
<tr>
<th>STRATIFY:</th>
<th>RADIATION (5 fx/wk)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEX</td>
<td>RADIATION (6 fx/wk)*</td>
</tr>
<tr>
<td>SIZE</td>
<td></td>
</tr>
<tr>
<td>DEPT.</td>
<td></td>
</tr>
</tbody>
</table>

*) Total 62-68 Gy / 2 Gy per fraction

An estimate will be made at the first follow-up of both the primary tumour and all lymph node metastases to be treated and of the acute irradiation reaction in the treated tissue. At the next control it will be examined whether recurring or persistent tumour is present in the irradiated area, both in the primary tumour area and in the regional lymph nodes. Any treatment of recurrences must be registered. Late radiation complications and distant metastases, if any, must likewise be registered. Survival (total and corrected) is the ultimate analysis aim in the study.
II - BEFORE TREATMENT

SELECTION OF PATIENTS
All patients with untreated loco-regional carcinoma in glottic larynx, can be included in the study, provided they fulfil the following criteria:

(1) The patient must - following verbal and written information - give his or her written informed consent to participate in the study (Appendix 1).
(2) The patient should not have known distant metastases.
(3) Tumour classified as clinical stage I-IV glottic laryngeal carcinoma according to the TNM classification (UICC, Geneva 1987) (19).
(4) Histopathologically verified diagnosis of invasive squamous cell carcinoma.
(5) The patient must be candidate for primary curative radiotherapy (alone), and be expected to accomplish the treatment (standard regimen).
(6) The patient should not be in a state or condition which could be expected to influence the outcome of the radiation treatment or complicate the assessment or the treatment control, or (apart from the present disease) reduce the life expectancy.
(7) The patient must not be pregnant.

EXAMINATIONS BEFORE START OF TREATMENT
The following should be registered:

(1) Histology and differentiation.
(2) TNM classification (UICC 1987), localisation and size of the primary tumour and regional lymph node metastases, evaluated by clinical examination, endoscopy and possibly scanning.
(3) Performance status (WHO criteria (20))
   0 Normal activity
   1 Symptoms, but almost normal activity
   2 Bedridden, but less than 50% of normal day-time
   3 Confined to bed for more than 50% of normal day-time
   4 Totally bedridden
(4) X-ray examination of thorax
(5) Weight
(6) Laboratory tests, as follow:
   - hemoglobin
   - P-albumin

Possibly examination for prognostic parameters ($T_{per}$, SF2-assay, oxygen measurement) (please see specific protocol).
INCLUSION AND RANDOMIZATION OF PATIENTS

After collecting the above-mentioned information an on study form is used to include the patient into the trial. On this form the following information is given:

- patient identification
- institution and investigator
- symptoms
- tumour localization and size
- tumour histology
- TNM classification
- haemoglobin before treatment
- performance status
- weight
- patient acceptance to participate in the trial
- other eligibility parameters

When the on study form has been filled in and the patient has accepted to participate in the trial the randomization is made by contacting the secretariat (between 8 a.m. and 3 p.m.)

Danish Cancer Society
Department of experimental clinical oncology
Radiumstationen
Nørrebrogade 44
DK - 8000 Aarhus C
Denmark
Phone: +45 86 12 06 45
Fax: +45 86 19 71 09

The patient is given a randomization number and is allocated to 5 or 6 fractions per week.

Note: Since it is important to register all patients, an on study form must be filled in, also if the patient does not fulfil the inclusion criteria for this protocol, or if the patient does not want to participate in the project.
III-TREATMENT

RADIOThERAPY

The patients are treated with curative radiotherapy given by Co-60 or linear accelerator. The treatment is given by photons or electrons at a dose level of 0.5 to 5 Gy per minute. Compensation must be used, and fixation of the patients is compulsory.

The primary target area includes primary tumour in T-position, allowing a margin of approx. 2 cm (at least 1 cm, depending on size of tumour and technique used). In case of involved palpable lymph nodes the neighbouring (more caudal) lymph node group is included in the primary target area, i.e. at least 3 cm distally from the lower part of the palpable lymph nodes.

The secondary target area in principle includes all macroscopic tumour tissue (primary tumour and possible lymph node metasteses with a margin of at least 1 cm).

DOSE

All fields are to be treated each time and the treatment technique must secure that the minimal absorbed target dose for photon fields constitutes at least 95% of the specified centrally absorbed dose.

For electron fields the absorbed median target dose is calculated as

\[ D_{T1 \text{ median}} = \frac{1}{2} (D_{T1 \text{ max}} + D_{T1 \text{ min}}). \]

The treatment is given in 5 or 6 fractions per week (see below), to a centrally absorbed target dose of 2 Gy per fraction.

The primary target area should be treated by at least 46 Gy in 23 fractions.

Medulla spinalis should not be treated by a larger total dose than 50 Gy, including any contribution from electron fields given to the secondary target field.

The secondary target field is treated according to size of tumour and/or size of lymph nodes (the larger of these). This is calculated based on the largest diameter at the start of treatment and the total (primary and secondary) target dose must be as follows (minimal doses):

- for tumours \( \leq 4 \) cm: 66 Gy/33 fractions
- for tumours \( > 4 \) cm: 68 Gy/34 fractions.

Small highly differentiated T1 glottic tumours may however be treated by 62 Gy given in 31 fractions.
If primary tumour (T-position) and lymph nodes (N-position) are included in the secondary target area, this is treated according to the guidelines given for the largest of the involved tumours.

FOR A DETAILED DESCRIPTION OF FIELDS AND RADIATION THERAPY, PLEASE CONSULT "DAHANCA GUIDELINES FOR RADIATION TREATMENT OF HEAD AND NECK CANCER".

FRACTIONATION

The patients are randomized to 5 or 6 weekly fractions of 2 Gy.

Patients randomized to 5 fractions per week are given 1 fraction per day, Monday through Friday.

Patients randomized to 6 fractions per week are given 1 fraction per day, Monday through Friday. The sixth fraction must be given on either the Saturday, or as an extra fraction on one of the first five weekdays, but always allowing at least a 6 hour interval.

Should an unintended interruption of the treatment occur, this missing treatment should be given as soon as possible, preferably within a week. This could be given either as an extra fraction Saturday, or by giving an extra treatment the same day as a planned fraction, allowing an interval of at least 6 hours. Compensation for a missed treatment should be given as soon as possible after the interruption of treatment has occurred, provided that the patient is expected to be able to cope with this. In the present protocol, it is of utmost importance that the planned treatment schedule be kept as strictly as possible. Unplanned interruptions in the treatment must thus be compensated as quickly as possible and preferably within the following week. The interval corrections used in former protocols are no longer valid.

EVALUATION OF PATIENTS DURING TREATMENT

The patients should be seen at least once a week during treatment. Time and severity of the acute irradiation reaction on mucosa and skin must be noted.

During treatment (after 4 weeks), at the end of treatment, and at the first follow-up (after 2 months) primary tumour response must be assessed (WHO criteria). This is estimated as: (1) progression (>25%), (2) unchanged, (3) partial reduction, (4) complete regression, (5) not assessable (20).

All data are registered on a study parameter and primary reaction form.

After end of radiotherapy, treatment data should be computer registered. For this purpose use primary treatment form.
VI - AFTER TREATMENT

PATIENT FOLLOW-UP
The patients must be seen two months after end of treatment. At this examination response and primary treatment complications are registered. The study parameter and primary reaction form is filled out.

The patients are then seen every third month the first 2 years, and then biannually for the following three years. At each post-treatment examination a follow-up and complication form is filled in.

At each post-treatment examination the following must be controlled:
1. Residual tumour or recurrence in T- and N-position within the treated area.
2. Recurrence outside the irradiated area.
   In case of recurrence or occurrence of distant metastases a recurrence form must be filled in.
3. Late complications to the treatment
4. In case of death, registration of date, cause, possible resection findings, and, if relevant, localisation of the residual cancer at time of death. This must be indicated on a death form.

TREATMENT OF RESIDUAL TUMOUR AND RECURRENCE
In case of residual tumour, recurrence or progression of disease the treatment will depend on the state of the individual patient, symptoms, and former treatment. The treatment is registered on the specific recurrence form. The patient remains in the study.

REGISTRATION AND COMMUNICATION
Registration of data is made by computer. A software system (Meclog) is provided to the involved departments. Storing, control, and up-dating of patient information will be performed locally and communication between centre and secretariat will take place in form of computer files.

The following forms/screen menus will be used for registration of data:

1. On study form
   This form is used to include the patient into the trial and holds patient identification, description of tumour, TNM-classification, laboratory tests, height and weight, and other criteria.

2. Primary treatment form
   Immediately after end of primary treatment this is filled in. To a certain degree the data is derived from the patient's treatment chart.
3. Study parameter and primary reaction form
   At the first follow-up examination (2 months after completion of treatment) final registration of primary response is made and all radiation reactions registered.

4. Follow-up and complication form
   To be used at each follow-up. It contains information about date of and status at the latest control, tumour response and complications.

5. Recurrence form
   To be used in case of recurrence. This form specifies recurrence, what has been undertaken and the result.

6. Death form
   To indicate final status when the patient dies.

STATISTICS
The study will be evaluated together with the DAHANCA 7-91 protocol, which comprises carcinoma of supraglottis, pharynx, and oral cavity.

The study will be closed after a total intake of 1,000 patients into the two protocols (DAHANCA 6 and DAHANCA 7), which is expected within 4 years, and finally evaluated after a minimum follow-up time of 18 months. If the true frequency of persistent loco-regional tumour control is changed by 15% (i.e. from 45% to 60%), the probability calculated by a double-sided test is greater than 99% for a significant difference (P < 0.05). If the true frequency of tumour control is changed by 10% (from 45% to 55%) the probability of observing a significant difference (P < 0.05) is greater than 85% for.

The final analysis of the study will include a univariate estimate of stratification parameters and other identifying conditions of importance for survival, recurrence-free survival, local control and complications. The inherent relationship between these parameters will be assessed by a multivariate analysis.

ANALYSES
Interim analyses of the two protocols will be made one year after start of the study and once yearly hereafter. The purpose of these is to detect larger differences in toxicity or response which might cause closure of the study. The result of the interim analyses will be blinded and communicated to the involved treatment departments only if important differences in the results indicate this.

A complete analysis will be performed ½, 1½, 3, 5, and 10 years after closure of the study, and whenever it in other ways is considered necessary. The analysis will include evaluation of local and regional control, survival, and complications.

All patients will be followed till death and once a year information will be obtained from the central person registry. A list of deceased patients will be presented to all treatment centres and the relevant patient files closed. The final closure will also serve as control of previously registered data.
PUBLICATION

Irrespective of the outcome of the study the results will be published. The authors are members of "DAHANCA Study Group" who have contributed actively to the accomplishment of the study. All others who have contributed substantially to the study may be co-authors. This does not prohibit an individual participant or department from publishing results regarding patients whom he or she has included into the study, albeit expected that the other participants in the study see the manuscript before publication and that such publication will not take place before the total material has been published.

Other information, that may be gained from this study, but otherwise not related to nimorazole and the effect of fractionation, can be used after mutual agreement with the other participants in the study.

ETHICS

The study is designed according to the requirements laid down by the Helsinki Declaration II. After careful considerations of the predictable risks, it is the responsible investigator's judgement that the project does not present ethical problems.

The protocol should be adapted to and approved by all relevant national or local ethical committees.
REFERENCES


APPENDIX 1

PATIENT INFORMATION DAHANCA 6-91

It has been confirmed by the medical examinations you been through that you have a tumour in the head and neck region. The best way to treat this disease is radiotherapy. This radiotherapy is given by one treatment every day, Monday through Friday, 5 treatments per week.

From experience we know that in course of the treatment you may suffer some side effects from the radiotherapy. This may be in form of irritation, pain and infections of the mucosa around the tumour. During the course of treatment we will examine effect and side effects. If needed, we will offer you medicine to reduce these side effects.

It is important that the planned radiation treatment is given with a minimum of interruptions. If the total treatment time is reduced, we may obtain a better treatment effect. A more intense treatment schedule may, however, result in an increased risk of side effects.

To find out which treatment is the most optimal, we should like to ask you to participate in a scientific study. If you accept to participate in the study we will by means of a randomization allocate you to one of the two possible treatments. It may either be:

1. our current treatment modality giving 5 radiation treatments per week, or

2. the new treatment modality giving 6 radiation treatments per week. This extra weekly treatment is achieved by giving radiotherapy twice on one of the first 5 weekdays allowing at least a 6 hour interval between the treatments. The total period of treatment is thus reduced by one week.

Whether you want to participate in the study or not, is up to you. If you decide to participate, we ask you to sign the present patient information. By doing this, you merely indicate that you have had verbal and written information about the study. The signature does not in any way oblige you. You may at any time decide to withdraw from the study, and your signature has no importance in that respect. We would then suggest that you continue the treatment receiving one treatment per day in 5 days. If you do not want to participate in the study, this will also be the treatment we offer you.

If you have any further questions, please do not hesitate to contact the department by phone (Phone: xx xx xx xx, extn. XXXX)

Yours sincerely,

<< >> <<>> <<>> M.D., Dept. of Oncology, <<>> <<>> Hospital.

Signature: ________________________________