A randomized multicenter study of 5 versus 6 weekly fractions of radiotherapy in the treatment of squamous cell carcinoma of the head and neck

International Atomic Energy Agency
- Clinical Research Project -
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# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTENTS</td>
<td>2</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>3</td>
</tr>
<tr>
<td>PURPOSE</td>
<td>5</td>
</tr>
<tr>
<td>OBJECTIVE AND DESIGN OF THE STUDY</td>
<td>6</td>
</tr>
<tr>
<td>BEFORE TREATMENT</td>
<td>7</td>
</tr>
<tr>
<td>PATIENT SELECTION</td>
<td>7</td>
</tr>
<tr>
<td>EXAMINATIONS BEFORE START OF TREATMENT</td>
<td>7</td>
</tr>
<tr>
<td>INCLUSION CRITERIA</td>
<td>7</td>
</tr>
<tr>
<td>EXCLUSION CRITERIA</td>
<td>8</td>
</tr>
<tr>
<td>RANDOMIZATION OF PATIENTS</td>
<td>8</td>
</tr>
<tr>
<td>TREATMENT PRINCIPLES</td>
<td>9</td>
</tr>
<tr>
<td>RADIOTHERAPY</td>
<td>9</td>
</tr>
<tr>
<td>TIME, DOSE AND FRACTIONATION</td>
<td>10</td>
</tr>
<tr>
<td>THE PATIENTS ARE RANDOMIZED TO 5 OR 6 WEEKLY FRACTIONS OF 2 Gy.</td>
<td>10</td>
</tr>
<tr>
<td>EVALUATION OF PATIENTS DURING TREATMENT</td>
<td>11</td>
</tr>
<tr>
<td>AFTER TREATMENT</td>
<td>11</td>
</tr>
<tr>
<td>PATIENT FOLLOW-UP</td>
<td>11</td>
</tr>
<tr>
<td>REGISTRATION AND COMMUNICATION</td>
<td>12</td>
</tr>
<tr>
<td>STATISTICS</td>
<td>13</td>
</tr>
<tr>
<td>ANALYSES</td>
<td>13</td>
</tr>
<tr>
<td>PUBLICATION</td>
<td>13</td>
</tr>
<tr>
<td>ETHICS</td>
<td>14</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>15</td>
</tr>
<tr>
<td>LIST OF PARTICIPATING INSTITUTIONS AND PRINCIPAL INVESTIGATORS</td>
<td>18</td>
</tr>
<tr>
<td>DECLARATION</td>
<td>19</td>
</tr>
<tr>
<td>APPENDIX 1:</td>
<td>20</td>
</tr>
<tr>
<td>CHECK-LIST FOR INCLUSION/EXCLUSION</td>
<td>20</td>
</tr>
<tr>
<td>APPENDIX 2:</td>
<td>21</td>
</tr>
<tr>
<td>DOCUMENT OF INFORMED CONSENT</td>
<td>21</td>
</tr>
<tr>
<td>APPENDIX 3:</td>
<td>22</td>
</tr>
<tr>
<td>DECLARATION OF HELSINKI</td>
<td>22</td>
</tr>
<tr>
<td>APPENDIX 4:</td>
<td>25</td>
</tr>
<tr>
<td>WHO PERFORMANCE STATUS</td>
<td>25</td>
</tr>
<tr>
<td>APPENDIX 5:</td>
<td>26</td>
</tr>
<tr>
<td>UICC TNM CLASSIFICATION (1997)</td>
<td>26</td>
</tr>
<tr>
<td>APPENDIX 6:</td>
<td>27</td>
</tr>
<tr>
<td>WHO HISTOLOGICAL TYPEING (1991)</td>
<td>27</td>
</tr>
</tbody>
</table>
Introduction

Squamous cell carcinoma in the head and neck region is becoming a still more frequent disease, and is now the fourth most common malignant disease worldwide. Characteristically this is a loco-regional disease confined to primary tumor (T) and regional lymph nodes (N), whereas distant metastases are rarely seen at time of diagnosis. Radiotherapy and surgery are thus the treatments of choice, with radiotherapy being the treatment modality if organ conservation is required.

One of the most important biological factors related to the outcome of radiotherapy in squamous cell carcinoma is associated with the proliferation of tumor cells during treatment. It has been well documented that a prolonged total treatment time may reduce the chance of tumor control, and a substantial number of clinical reports indicate that a reduction in overall treatment time may result in improved tumor control (Withers et al. 1988, Overgaard et al. 1988, Fowler & Lindstrom 1992). A shorter treatment time (accelerated fractionation) can be obtained by applying a higher dose per fraction, but this will result in a disproportionate increase in the incidence of late complications (Thames et al. 1989, Bentzen 1993). Accelerated fractionation is thus possible only if the weekly number of fractions be increased without increasing the dose per fraction.

Experience has especially been gained from three treatment schedules (Peters et al. 1988, Overgaard 1993, Ang 1997, 1998). A continuous, very short schedule (CHART) giving 54 Gy in 36 fractions in 12 consecutive days, 3 times a day with an interval of 6 hours (Dische et al. 1997). A schedule with 2 weeks' treatment of 2 fractions per day, followed by a 2 week break, followed by one week of treatment (accelerated split-course) (Horiot et al. 1997). Despite the break, the total treatment time is reduced from approx. 7 weeks to 5 weeks. Due to fierce acute mucosal reactions 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. The CHART regimen is based on finishing the treatment before the mucosal reactions set in. Multiple daily fractions require a sufficient interval (6 hours or more) between the two treatments to allow repair of radiation-induced normal tissue damage. A third treatment principle is concomitant boost (Peters et al. 1988), 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). During the
last 7-10 days of treatment 2 fractions per day are applied resulting in a 1-1½ weeks reduction in overall time. In the last part of the treatment the patients will experience fierce acute reactions.

Some large randomized studies of accelerated fractionation principles have recently been completed. The MRC studied CHART versus conventional radiotherapy (Dische et al. 1997). Although no overall difference was observed in head and neck, the result demonstrate that the total dose can be reduced if the overall treatment time is also reduced, which confirms that dose may be traded for time. The EORTC 22851 randomized trial compared conventional radiotherapy (70 Gy / 35 fractions / 7 weeks) with 72 Gy / 45 fractions / 32 days given as accelerated split-course. In this study a significant increase in loco-regional control was obtained, but at the expense of a significant increase in both acute and (consequential) late morbidity (Horiot et al. 1997). The Danish DAHANCA 7 trial compared two strategies with the same total dose (66 Gy in 33 fractions) given with either 5 or 6 fractions per week (Overgaard et al. 1997, 1998). This was done by reintroducing treatment on Saturdays, or by giving an extra fraction on another of the normal treatment days (providing at least a 6 hours 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 that is 8 days shorter than that of the conventional schedule. By an expected repopulation corresponding to 0.5 Gy/day, this will in principle result in a treatment regimen that is approx. 4 Gy "hotter" than that formerly used. This should correspond to an expected treatment benefit of approx. 15% depending on the heterogeneity of the patient population. The latter is important, since it has become increasingly clear that some heterogeneity exist, and not all patients may benefit from a reduced overall treatment; and certainly not if this is associated with a reduced total dose. Especially poorly differentiated tumors may suffer form this problem (Hansen et al. 1997). A better understanding of tumor heterogeneity and identification of patients who may benefit from accelerated treatment is strongly needed. Until this is known, we must consider that a reduced total dose may include the risk of undertreating some tumors. The DAHANCA 7 showed a significant benefit of 15% in loco-regional control. Also, the acute side effects were increased, but the late morbidity was not significantly different. Another study with the same rationale was reported by Maciejewski et al. (1996) and consisted on randomizing patients with head and neck cancers between 7 weekly radiation treatments of 2
Gy each versus the conventional 5 weekly fractions of 2 Gy each. They found an unacceptable high rate of acute and consequential late complications in the 7-day arm. These authors are now testing a similar regimen using a smaller fraction size of 1.8 Gy per fraction. The Vancouver Cancer Centre tested acceleration by giving two daily fractions of 2 Gy compared to conventional treatment in a phase III trial (Jackson et al, 1997). Grade 3 and 4 acute toxicity was significantly higher in the accelerated arm leading to closure of the study after accrual of 82 patients. There was no difference in tumor control. Finally, the RTOG 90-03 compares conventional therapy with accelerated split-course with concomitant boost. This study is still recruiting (Ang 1997, 1998).

Thus, repopulation is important, and a reduced treatment time may yield a better tumor control, provided the total dose is not reduced. Such a regimen may also result in increased acute radiation morbidity, and can not be accepted as routine, without prior documentation in broad based controlled clinical trials performed in the healthcare environments where it is going to be carried out. The DAHANCA 7 study, which was performed in a well-defined Danish patient population, documented a improved tumor control and an acceptable level of complications. Such treatment does not require additional resources, and is therefore the basis for this trial.

**Purpose**

The purpose of the present study is to improve the effect of radiotherapy given to patients with head and neck carcinoma, who are candidates for primary radiotherapy alone. The protocol seeks to establish the importance of 5 vs. 6 weekly fractions of 2 Gy given to the same total dose. The trial will be stratified in order to evaluate the potential relationship between histopathological differentiation and overall treatment time. The study will evaluate the loco-regional tumor control after radiotherapy, disease-free and overall survival, and the early and late treatment related morbidity. The protocol intends to exclude a minimum of patients to get a true impression of the suitability of such therapy in an unselected patient population.
Objective and design of the study

The aim of the study is to determine the possible therapeutic gain obtained by reducing the overall treatment time in the radiation treatment of patients with head and neck cancer who are candidates for primary external radiotherapy alone. The protocol seeks to establish the importance of 5 vs. 6 weekly radiotherapy fractions of 2 Gy given to the same total dose.

The study design is a stratified, balanced, and randomized study (phase III) of patients with Stage I-IV squamous cell carcinoma of the pharynx (except nasopharynx and stage I glottic carcinoma), larynx and oral cavity.

The study randomizes to 5 versus 6 fractions per week and the stratification is based on the following parameters:

- tumor stage: T1-2, T3-4
- tumor localization: oropharynx/hypopharynx/larynx, oral cavity
- histological differentiation (grade): poor, moderate/well, unknown
- institution

The latter three study end-points will be recorded at regular follow-up visits for at least 5 years after randomization or until death of the patient.
Before treatment

Patient selection

Patients with loco-regional squamous cell carcinoma in pharynx (except nasopharynx and stage I glottic carcinoma), larynx and oral cavity can be included in the study. Prior or planned surgical excision excludes patients from the study.

Examinations before start of treatment

(1) Histopathology and differentiation of primary tumor (WHO criteria).

(2) TNM classification (UICC/AJC 1997), localization and size of the primary tumor and regional lymph node metastases evaluated by clinical examination, endoscopy, relevant radiographs and/or CT scan and/or ultrasound.

(3) Performance status (WHO criteria).

(4) Chest X-ray.

(5) Hemoglobin.

(6) Complete oral and dental evaluation and management.

(7) Photographic documentation (optional).

Inclusion criteria

(1) Tumor classified as stage I-IV located in oropharynx, hypopharynx, larynx (not glottic stage I), or oral cavity according to the TNM classification (UICC/AJC 1997).

(2) Histopathological diagnosis of invasive squamous cell carcinoma in the primary tumor.

(3) Age ≥ 18 years.

(4) Informed consent according to the Helsinki declaration II and local regulations.

(5) The patient must be candidate for external beam radical radiotherapy, and must be expected to accomplish the treatment.

(6) Performance status 0-2 according to WHO criteria.
**Exclusion criteria**

(1) Distant metastases.
(2) The patient should not be in a state or condition that could be expected to influence the outcome of treatment, or complicate the assessment or the treatment follow-up, or (apart from the present disease) reduce the life expectancy.
(3) Surgical excision (except biopsy), prior or planned.
(4) The existence of synchronous multiple malignancies (not leukoplakia).

**Randomisation of patients**

After collecting the above-mentioned information, the **On Study Form** is used to include the patient into the trial. On this form the following information is given:
- patient identification, sex, weight, performance status, hemoglobin, presence of leukoplakia, smoking and chewing habits.
- tumor localization, TNM classification, T-size, N-size, histopathology, differentiation, planned radiation dose and technique.

When the **On Study Form** has been filled in, and the patient is found to meet **all** criteria for inclusion in the study, the randomization is made by giving this information to the secretariat by fax or **e-mail** at the following address:

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*Denmark*

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*Fax: +45 86 19 71 09*

*E-mail: deco@onko.aau.dk*

The randomization details are provided a.s.a.p. by fax. The secretariat is open Monday-Friday between 7 am and 2 pm GMT.
Treatment principles

Prior to treatment all patients should undergo oro-dental evaluation with revision of all potential infectious foci. Dental care including caries prophylaxis is recommended during and after radiotherapy.

Radiotherapy

The patients are treated with external radiotherapy based on Co-60 or linear accelerator. The treatment is given by photons or electrons at a dose rate of 0.5 to 5 Gy per minute. Missing tissue compensation or equivalent wedges should be used, and fixation of the patient is compulsory. The used equipment should have the dosimetry verified through the IAEA SSDL Network or equivalent quality control service, e.g. EQUAL.

The treatment principles and dose specifications should follow the guidelines given in the ICRU-50 report.

The clinical target volume (CTV), or “large fields”, includes primary tumor in T- and N-position, allowing a margin of approximately 2 cm (at least 1 cm, depending of size of tumor and technique used). In case of involved palpable lymph nodes, the neighboring (more caudal) lymph node group is included in the clinical target volume area, i.e. at least 3 cm distally from the lower part of the palpable lymph nodes (Figure 2).

The gross tumor volume (GTV), or “boost fields”, includes only macroscopic tumor tissue, i.e. the primary tumor and possible lymph node metastases with a margin of at least 1 cm.

All fields must be treated each time and the treatment technique must secure that the minimal absorbed target dose for photon fields constitutes at least 95% and not more than 105% of the specified centrally absorbed dose. The dose is specified in the ICRU reference point, i.e. for

_**single field:**_ the central axis in the specified depth
parallel opposing fields: the midpoint on the central axis
non-opposing fields: the intersection of the central axes

The dose is calculated in water including missing tissue compensation.

For electron fields the target volume should be encompassed in at least the 85% isodose.

Each department is requested to make their own detailed treatment specifications, taking the available equipment and resources into consideration. These specifications should contain description of the field arrangements and dose calculations used for treatment of different tumor sites. Each field arrangement should be specified by a number, which is used for reporting on the Treatment Form. A copy of these specifications should be submitted to the secretariat as soon as possible, preferably before patients are included.

**Time, dose and fractionation**

The treatment is given in 5 or 6 fractions per week, to a centrally absorbed target dose of 2.0 Gy per fraction. The CTV dose must be at least 44 Gy. The spinal cord should not receive a larger total dose than 50 Gy, including any contribution from electron fields in the second part of the treatment. The GTV is treated to a dose of 66-70 Gy in 33-35 fractions.

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<tr>
<th>Arm A</th>
<th>66 Gy / 33 fx / 45 days</th>
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<td>Arm B</td>
<td>66 Gy / 33 fx / 38 days</td>
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**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 (or similar).

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 hours interval. Should an unintended interruption of the treatment occur, this missing treatment should be given as soon as possible, and preferably within the same or following 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. The maximum dose over any seven day period should not exceed 14 Gy. 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.

Evaluation of patients during treatment
The patients should be seen at least once a week during treatment. Time and severity of the acute irradiation reactions in mucosa and skin must be noted. These data are registered on the Treatment Response Form.

After treatment

Patient follow-up
The patients must be seen 1-2 months after the end of treatment to record persistent acute toxicity and early tumor response. Afterwards, the patients are seen every 3 months for 2 years, and then biannually for the following three years. In a large multi-center study like this, it is of utmost importance that patient follow up is effective. If the loss to follow-up is 10% or more, it might jeopardize any meaningful evaluation of the results. At each post-treatment examination a Follow-up Form is filled in with data on overall loco-regional control and late complications of the treatment. In case of treatment failure, death, completion or loss of follow-up, or new primary tumor, an Event Form is filled in with data on treatment status, type of event, specification of any salvage treatment, and vital
status.

**Registration and communication**

The completed data forms are faxed to the secretariat, where the data is computerized for scientific analysis. The original documentation forms should be kept by the treating institution.

The following five forms will be used for registration of data:

1. **On Study Form**
   - This form is used to include the patient into the trial and holds all data necessary for inclusion and randomization.
   - *fax or e-mail at time of randomization*

2. **Treatment Form**
   - Information on the applied radiotherapy.
   - *fax/mail completed form no later than the time of first follow-up (2 months after treatment)*

3. **Treatment Response Form**
   - Weekly data on acute toxicity.
   - *fax/mail completed form at time of first follow-up (2 months after treatment)*

4. **Follow Up Form**
   - This form is used at each follow-up. It contains data on tumor response, treatment sequelae and death.
   - *fax after each visit, but continue recording on the same form*

5. **Event Form**
   - Use in the event of recurrence, death, new primary tumor, completion or loss of follow-up.
   - *fax new form at time of each event*
**Statistics**

The study will be closed after a total intake of 1,000 patients into the two arms, which is expected within 3 years. If the true frequency of persistent loco-regional tumor 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 tumor control is changed by 10% (from 45% to 55%) the probability of observing a significant difference ($p < 0.05$) is greater than 85%. The final analysis of the study will include a univariate estimate of stratification parameters and other conditions of importance for survival, disease-free survival, local control and complications. The inherent relationship between these parameters will be assessed by multivariate analysis.

**Analyses**

Interim analyses of the protocol will be made one year after start of the study and at regular intervals (e.g. 18 months) hereafter. The purpose of this is to detect important differences in toxicity or response (overall or within individual institutions) which might cause closure or modification of the study. The results 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 1, 3, and 5 years after closure of the study, and whenever it in other ways is considered necessary. The analysis will be performed for all randomized patients on an intention to treat basis, and will include evaluation of local and regional control, crude and disease free survival, and complications.

**Publication**

Irrespective of the outcome of the study the results will be published. Each publication will originate from the Clinical Trials Unit of the Danish Cancer Society, Department of Experimental Clinical Oncology, and will name all the participating institutions. The chief responsible member of each participating department is co-author of the publication, provided that they contribute with at least 5% of the total number of patients. Each participating institution can use the material for regional information in lecture form by mentioning the name of all participating
institutions after the initial publication of the entire material. Local partial projects can be published by the respective responsible member(s) after the initial publication of the entire material.

In all publications, the IAEA support and initiative will be acknowledged.

**Ethics**

The study is designed according to the requirements laid down by the Helsinki Declaration II. After careful considerations of the predictable risks and potential benefits, it is the responsible investigator's judgement that the project does not present ethical problems. All relevant national and/or local ethical and protocol review committees should approve the protocol.
References


ICRU Report 50 (1993), *Dose specification for reporting external beam therapy*. International Commission on Radiation Units and Measurements, Bethesda, Maryland, USA.


Horiot, J.C., Bontemps, P., van den Bogaert, W., Le Fur, R., van den Weijngaert, D., Bolla, M., Bernier, J., Lusinchi, A., Stuschke, M., Lopez-Torrecilla, J., Begg, A.C., Pierart, M. & Colette, L. (1997): Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother Oncol, 44: 111-121.

Maciejewski, B., Skladkowski K., Pileck, B. (1996) Randomized clinical trial of accelerated 7 days per week fractionation in radiotherapy for head and neck cancer: Preliminary


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Declaration
### Appendix 1:

**Check-list for inclusion/exclusion**

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1. Stage I-IV oropharynx, hypopharynx, oral cavity or stage II-IV larynx
2. Histologically verified squamous cell carcinoma
3. Distant metastasis
4. Age $\geq$ 18 years
5. Informed consent
6. Candidate for definitive radiotherapy
7. Prior or planned surgical excision (except biopsy)
8. Performance status 0-2 (WHO)
9. Chest x-ray performed
10. Multiple synchronous malignancies (not leukoplakia)
Appendix 2

*Document of informed consent* *

With my signature below I confirm that I have been informed about my participation in a clinical research study. This study examines the value of giving radiotherapy in a shorter overall treatment time in the treatment of head and neck cancer. Patients in this trial are allocated to one of two different treatments:

1. Standard radiotherapy given with 5 fractions per week
2. The same radiotherapy dose given with 6 fractions per week

I know that my treatment will be randomly chosen to one of these treatments.

I have been informed about possible side effects from this treatment, which include mucositis, pain, dysphagia, fibrosis and edema.

All records of this treatment and examinations will be handled confidential. Only medical staff involved in my treatment, and a representative of the Clinical Trials Unit, have the right to inspect my record or me.

Emergency treatment of any injury will be provided by the institution. Compensation for study related injury will not be provided by the institute.

The person to ask study related questions:

_________________________________________________________

(Name) __________________ (Telephone) ___________________

I know that my participation in this trial is voluntary. My refusal to participate will involve no loss of benefits or penalize my care. A discontinuation of my participation will involve no loss of benefits to which I am entitled.

This has been explained to me in a language that I understand.

_________________________________________________________

(City)  (Date)  (Signature of patient)  (Name in print)

*SUGGESTION, TO BE ADAPTED TO LOCAL REQUIREMENTS*
Appendix 3

Declaration of Helsinki

Recommendations guiding physicians in biomedical research involving human subjects.

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, and the 41st World Medical Assembly, Hong Kong, September 1989.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without direct diagnostic or therapeutic value to the person subjected to the research. Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, The World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the law of their own countries.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.2. The design and performance
of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or others. Concern for the interests of the subject must always prevail over the interest of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subjects and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed on the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent in duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with
national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with professional care (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of the person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

III. Non-therapeutic biomedical research involving human subjects.
Appendix 4

**WHO Performance Status**

O: Able to carry out all normal activity without restriction.

1: Restricted in physically strenuous activity, but ambulatory and able to carry out light work.

2: Ambulatory and capable of self-care but unable to carry out any work; up and about more than 50% of waking hours.

3: Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.

4: Completely disabled; cannot carry out any self-care; totally confined to bed or chair.
Appendix 5:

*UICC TNM classification (1997)*
Appendix 6:

**WHO histological typing (1991)**