Randomized trial on chest irradiation in extensive
disease small cell lung cancer

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1 Background and introduction

Chemotherapy is the cornerstone in the treatment of extensive disease small cell lung cancer (ED-SCLC), and four to six cycles of chemotherapy without maintenance therapy is current standard [Felip, 2007]. However, survival in patients presenting with ED-SCLC is poor and has shown little improvement in the past few decades. An analysis of SEER data revealed the 2-year all-cause survival in 2000 was still below 5% [Govindan 2006].

Recent trials using platinum-based chemotherapy in ED-SCLC show a time-to-progression of 4-6 months, and a median survival of 9-11 months [Socinski 2006]. Many approaches have been evaluated in an attempt to improve upon survival in SCLC, but most have not shown to be of benefit. These include maintenance chemotherapy [Schiller 2002], new chemotherapeutic agents [Hanna 2006], maintenance therapy using the metalloproteinase inhibitor marimastat [Shepherd 2002] and immunotherapy [Giaccone 2005]. The notable exception was the survival benefit reported in a phase III EORTC trial evaluating prophylactic cranial irradiation (PCI) versus no PCI following any response to induction chemotherapy [Slotman 2007]. Symptomatic brain metastases were significantly more frequent in controls (40% versus 15%), more of whom also died of SCLC (80% versus 68%). More patients in the PCI arm also received salvage chemotherapy at the time of disease recurrence. PCI is the new standard of care in all patients with SCLC who respond to chemotherapy.

Intrathoracic tumor control is a major problem in ED-SCLC. Over 75% of patients have persisting intra-thoracic disease after initial chemotherapy, and about 90% manifest intra-thoracic disease progression at 1 year after completing initial chemotherapy [Slotman,2007].

In a trial reported by Jeremic et al., patients with ED-SCLC who had a complete response at sites of distant disease, were randomized to thoracic radiotherapy (54 Gy in 18 days) in combination with low dose chemotherapy or an additional four cycles of cisplatin/etoposide chemotherapy only [Jeremic 1999]. A total of 109 patients were randomized after induction chemotherapy, and the reported median (17 versus 11 months) and 5-year survivals (9.1% vs 3.7 %) was far higher than has been reported by any other group for ED-SCLC. This study has not yet been repeated.

In the absence of promising systemic agents that can improve local response, a logical step would be to evaluate the role of thoracic irradiation in patients with ED-SCLC who respond to chemotherapy.
2 Objectives of the trial

2.1 General objectives
The objective of this study is to investigate whether thoracic radiotherapy can improve 1-year survival in patients with extensive disease SCLC, following a response to chemotherapy, from 27% to 37%, as measured from time of randomisation after chemotherapy.

2.2 End-points
The primary end-point of this study is survival. The secondary end-points of this study are pattern of failure (thorax, brain, other) and toxicity.

3 Patient selection criteria

3.1 Inclusion criteria
- Cytologically or histologically proven small cell lung cancer
- Documented extensive disease (see appendix E) before the start of chemotherapy
- Any response after 4 to 6 cycles of initial chemotherapy (chemotherapy regimen and response evaluation according to the standard institution policy, provided that none of the existing lesions progressed)
- Chemotherapy (preferably platinum-etoposide; other regimens need approval of study-coordinator) completed
- Maximum delay of 4 weeks between last chemotherapy administration and randomization
- No evidence of brain metastases or leptomeningeal metastases (A contrast enhanced CT MRI scan of the brain is mandatory in case of clinical suspicion of brain metastases)
- No evidence of pleural metastases or pleuritis carcinomatosa
- No prior radiotherapy to the brain
- No prior radiotherapy to the thorax
- Age 18 years or older
- Performance status 0 to 2 (WHO scale, see Appendix B)
- Patient must be willing to receive chest irradiation
- Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations
- Volume should be encompassable in acceptable radiation fields

3.2 Exclusion criteria
None
4 Trial design

This is a multicenter phase III randomized trial, aiming at demonstrating a difference in overall survival between the two arms. Patients with cytologically or histologically proven ED small cell lung cancer will be treated with chemotherapy, according to the standard treatment policy of each participating center; chemotherapy is not part of the present protocol treatment. Response to chemotherapy will be evaluated according to the participating center's current practice. Patients with a response, who satisfy the other eligibility criteria listed in paragraph 3, will receive prophylactic cranial irradiation and will be randomized to receive either thoracic irradiation or no further therapy.

![Diagram](attachment:image.png)

All patients will receive PCI
5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Radiotherapy

5.1.1 Radiation scheme
For prophylactic cranial irradiation, the following schemes are acceptable: 20 Gy in 5 fractions or 30 Gy in 10 fractions 4-5 times per week. Each investigator should specify the details of the PCI schedule to the study-coordinator before randomizing patients to the trial.
For thoracic radiotherapy, 30 Gy will be delivered in 10 fractions, 4-5 times per week.

5.1.2 Treatment details
A linear accelerator with a photon energy of 4-10 MV will be used. Higher energies are only allowed in case a treatment planning system with advanced algorithm is being used.

The PTV for PCI includes the intracranial contents. Two opposed lateral fields will be used. Each field will be treated daily. The dose will be specified in the midline.

The PTV for thoracic radiotherapy includes the post-chemotherapy volume (GTV) with a margin of 15 mm. The initially positive hilar nodes and initially positive mediastinal nodal stations are always included, also in case of a complete response (CR). In general, parallel-opposed (AP-PA) fields can be used. If this will lead to anticipated severe toxicity, a conformal plan using planning CT-scan is indicated to keep the V20 below 35%. In all treatment planning, lung correction is required.

5.1.3 Timing of radiotherapy
PCI and thoracic radiotherapy will commence within six weeks after the completion of chemotherapy.
However, PCI and thoracic radiotherapy can only start at least 2 weeks after the last administration of chemotherapy, when the acute Grade 2 or higher toxicity of chemotherapy has resolved.

5.1.4 Expected toxicity
Expected acute toxicity using this thoracic radiotherapy schedule includes dysphagia, dyspnea, malaise, and/or cough [Kramer 2006].

5.1.5 Treatment in case of relapse or progression
In case of relapse or progression, the patient will be treated according to each center’s policy. This will not be part of the protocol therapy. Those patients will however continue to be followed for other relapses until death.
6 Clinical evaluation and follow-up

6.1 Before randomization
- Evaluation of patient eligibility
- Complete history and physical examination
- Chest X-ray

6.2 During radiotherapy
Acute toxicity will be recorded during treatment, and reported on the acute toxicity checklist and at end of treatment, according to CTCAE v 3.0 (http://ctep.cancer.gov/reporting/ctc.html).

6.3 After randomization / end of radiotherapy
Patients will be followed up at 6 weeks and at 3, 6, 9 and 12 months after randomization in both arms, and, subsequently every 6 months. This follow-up schedule must adhere to all patients, in both treatment arms.
The following examinations will be performed at each follow-up:
- Medical history and physical evaluation
- Chest X-ray

7 Criteria of evaluation

7.1 Primary endpoint
The primary endpoint is survival. Survival will be measured from date of randomisation.

7.2 Secondary endpoints
The secondary endpoints are local control, pattern of failure and toxicity (measured on the International Common Toxicity Criteria, version 3.0, see 6.2). Local control is defined as the absence of disease progression in the treated lobe/lung.
8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size
It is expected that 1 year survival in this group of patients is 27% from time of randomization [Slotman, 2007]. The primary end-point of this trial is to achieve an increase in 1 year survival of 10% (from 27% to 37%; HR=0.76). If we presume a 5% drop between randomisation and end of treatment, a total of 483 patients have to be randomized to obtain a 80% power against this expected difference (two-sided alpha=0.05).

Based on data from the Dutch Cancer Registry, in the Netherlands there will be about 600 new patients with 25% dying before the end of chemotherapy and about 70% having a “good response”. As a result, 300-325 patients will be eligible for this study per year. It is expected that centres from the UK and Belgium will also join the increase accrual.

8.1.2 Randomization and stratifications
It is recommended to refer the patient to the radiation oncologist during chemotherapy to enable timely randomization and start of treatment. Patients will be centrally randomized (for practical details, see chapter on randomization procedure). A minimization technique will be used for random treatment allocation stratifying by institution, and presence of intrathoracic disease.

8.2 Analysis
The principal end-point is median survival. The Kaplan-Meier method will be used to estimate survival at different time points, and the logrank two-sided test will be used to compare therapeutic arms according to the intent to treat policy. All randomized patients will be included in this analysis. Compliance to the intended radiotherapy schedule will be summarized by the following parameters: proportion of patients who completed the thoracic radiotherapy, reasons for non completion, proportion of patients for whom thoracic radiotherapy had to be delayed, and reasons for delays. All patients randomized in the radiotherapy arm will be included in this analysis. Toxicity will be reported for patients in both study arms.

8.3 Interim analyses
No interim analyses are foreseen in this trial. No independent data monitoring committee has been appointed for this study. Toxicity data will be reported to and evaluated by the study coordinator.
9 Investigator authorization procedure

Investigators will be authorized to register or randomize patients in this trial only when they have returned to the study investigator:

- a commitment statement / study acknowledgment form, indicating that they will fully comply with the protocol, to include an estimate of their yearly accrual and if any conflict of interest may arise due to their participation in the trial,
- a copy of the letter of acceptance of the protocol by their local or national (whichever is applicable) ethics committee,
- a signed conflict of interest disclosure form: this document will be required only if a possible conflict is declared by the commitment form.

Before registering their first patient, investigators also need to return to the IKA trial office a form specifying:

- the radiotherapy schedule that will be used for PCI,
- whether it is part of their center policy to perform a contrast enhanced CT and/or MRI scan of the brain before the start of chemotherapy,
- their policy on the use of CT and/or MRI of the brain after chemotherapy in asymptomatic patients,
- their policy on the use of CT and/or MRI of the brain at extracranial relapse in asymptomatic patients,
- their policy on the use of CT and/or PET scanning of the thorax for evaluating thoracic relapse.

This form should be appended to the commitment statement / study acknowledgment form.
10 Patient randomization procedure

A patient can be randomized by telephone to the IKA trial office from 8.30 am to 5.00 pm (Dutch local time) Monday through Friday. This must be done before the start of the protocol treatment.

Telephone: +31-20-3462544
or fax a completed randomisation form to +31-20-3462579
or e-mail: trialbureau@ikca.nl;
Confirmation of randomisation result will be sent by email

An exhaustive list of questions to be answered during the randomization procedure is included in the registration checklist, which is part of the case report forms. This checklist should be completed by the responsible investigator before the patient is randomized.

Standard questions
- institution number?
- name of the responsible investigator?
- patient's initials (maximum 4 letters)?
- patient's chart number (if available)?
- patient's birth date (day/month/year)?

Protocol specific questions
- eligibility criteria? All eligibility criteria will be checked;
- stratification factors?
- date of written informed consent?

At the end of the procedure, the treatment will be randomly allocated to the patients, as well as a patient sequential identification number. This number and the allocated treatment have to be recorded on the randomization checklist, along with the date of randomization. The completed checklist must be signed by the responsible investigator and returned to the data center with the initial data of the patient. The sequential identification number attributed to the patient at the end of the randomization procedure identifies the patient and must be reported on all case report forms.
11 Forms and procedures for collecting data

11.1 Case report forms and schedule for completion

Data will be reported on the forms and sent to:
IKA trial office,
P.O. Box 9236,
1006 AE AMSTERDAM,
The Netherlands

Most likely, an electronic CRF system will also be available to ensure fast data transfer with less mistakes.

Case report forms must be completed according to the following schedule:
A. Before the treatment starts:
   • the patient must be registered/randomized by the datamanager
   • the following set of forms has to be returned to the datamanager:
     o the Pre-Randomization Form/Registration Check-list
     o the On-Study form

The optimal way to work is to complete the Pre-randomization form, and to register/randomize the patient as soon as data are complete. The date of registration and patient sequential identification number are then completed on the check-list, and the whole set can be sent to the datamanager.

B. At the end of radiotherapy
   • the End of PCI radiotherapy form (both arms)
   • the End of Chest radiotherapy form (Chest radiotherapy arm only)

C. After the end of treatment
   • the follow-up form has to be sent at 6 weeks, 3 months, 6 months, 9 months, 12 months after randomization and subsequently every 6 months up to three years.

D. Upon occurrence of a Serious Adverse Event
   • In the control-arm: all Serious Adverse Events occurring within 110 days after randomization must be reported to the IKA trial office
   • In the chest irradiation-arm: all Serious Adverse Events at least probably related to the treatment occurring during the treatment period and within 90 days after the end of the last treatment must be reported to the IKA trial office. All serious adverse events must be reported by fax to the IKA trial office within 48 hours. FAX +31-20-3462579

ALL FORMS MUST BE DATED AND SIGNED BY THE RESPONSIBLE INVESTIGATOR OR ONE OF HIS/HER STAFF MEMBERS

11.2 Data flow
The case report forms must be completed, dated and signed by the investigator or one of his/her staff members as soon as the requested information is available.
In all cases, it remains the responsibility of the investigator to check that original case report forms are sent to the IKA trial office and that they are completely and correctly filled out. The original copy must be immediately returned to the IKA trial office and the investigator must keep a copy. Regular consistency checks on the CRFs will be performed and Query Forms will be issued in case of inconsistent data. Those Query Forms must be immediately answered and signed by the investigator and returned to the IKA trial office as soon as possible.

11.3 Control of data consistency
Data will be entered in the e CRF database. In case of paper forms this will be done by a double data entry procedure. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager to be entered on the master database. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.
12 Reporting adverse events

12.1 Definitions
Adverse Events (AE) are any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following the administration of the trial medication regardless of the dose or causal relationship. This can include any unfavourable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the trial treatments.

Serious Adverse Events (SAE) are defined as any undesirable experience occurring to a patient, whether or not considered related to the study treatments. Adverse events which are considered as serious are those which result in:

- Death. REMARK: In this study, death due to progression of disease will not be considered as an SAE and must, therefore, not be reported as an SAE.
- Life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- Hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above).

12.2 Reporting procedure of Serious adverse events
12.2.1 For patients in the control-arm
Only protocol-related serious adverse events, occurring within 110 days after randomization, must be reported on an SAE Form. This form must be faxed within 48 hours of the initial observation of the event.

12.2.2 For patients in the irradiation-arm
All serious adverse events, occurring during the treatment period and within 90 days after the last protocol treatment, must be reported on an SAE Form to the IKA Trial Office. Any late serious adverse events, occurring after this 90-day period, and at least possibly related to treatment, should follow the same reporting procedure. This SAE Form must be faxed within 24 hours of the initial observation of the event. The investigator will decide if these events are related to the study treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the Serious Adverse Event form.

The investigator will decide if these events are related to the study treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the Serious Adverse Event forms.

The assessment of causality is made by the investigator using the following definitions:

Relationship Description
UNRELATED There is no evidence of any causal relationship
UNLIKELY There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient’s clinical condition, other concomitant treatments).

POSSIBLE There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant treatments).

PROBABLE There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

DEFINITELY There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

NOT ASSESSABLE There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.
13 Ethical considerations

13.1 Patient protection
The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ref: http://www.ifpma.org/pdfifpma/e6.pdf). The protocol will by approved by the Local, Regional or National Ethics Committees.

13.2 Subject identification
The name of the patient will not be asked for nor recorded at the datamanager. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient’s initials (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

13.3 Informed consent
All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient’s subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized. This must be done in accordance with the national and local regulatory requirements.

The informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that “the written informed consent form should be signed and personally dated by the patient or by the patient’s legally acceptable representative”.
14 Administrative responsibilities

14.1 The study coordinator
The Study Coordinator will be responsible for writing the protocol, reviewing all case report forms and documenting his/her review on evaluation forms, discussing the contents of the reports with the datamanager of the IKA Trial Office, and for publishing the study results. He will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

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15 Publication policy

The final publication of the trial results will be written by the Study Coordinator on the basis of the final analysis. Draft manuscript(s) will be prepared by the study-coordinator and submitted to the co-authors. Authors of the manuscript will include at least the Study Coordinator, the investigators who have included more than 5% of the eligible patients in the trial (by order of inclusion). Authors of abstracts will include at least the Study Coordinator and the investigators who have included more than 10% of the eligible patients in the trial (by order of inclusion).

All manuscripts will include an appropriate acknowledgment section, mentioning all investigators and/or centers who have contributed to the trial, as well as supporting bodies.

16 Financing of data management

Funding for data management in the Netherlands has been obtained by a grant of the Dutch Cancer Society (KWF)
17 References


Appendix A : Informed Consent document
This is a clinical trial. Clinical trials include only patients who choose to take part. Please take your time to make your decision.

Randomized trial on chest irradiation in extensive disease small cell lung cancer (CREST-study)
Invitation to participate in the study

We have initiated a research study on patients that have a disease similar to yours. The study will be conducted under the supervision of physicians recognized as experts in this field of medicine. Today, you will be invited to take part to this research project after you are given full information about the study. You have received chemotherapy for a lung tumor. After this treatment, a good regression of tumor has been achieved. Patients like you treated for small cell lung cancer have a risk of recurrence or progression of the tumor in the lung, spreading into the brain. In this study, we will investigate whether giving a local irradiation to the tumor area in the lung, can reduce this risk. You are kindly invited to participate in this study. Possible side-effects include fatigue, dyspnea, coughing, nausea and vomiting,

**The chest irradiation consists of 10 daily fractions of radiotherapy, given over a period of 2 weeks.**
In this study, we investigate whether survival can be improved by adding chest irradiation. Should you decide not to take part in this trial this will not effect your further treatment and we advise you to have a standard treatment which is given in your institute. Your doctor will advise you about this.

**Voluntary participation**
Your participation in this research trial is entirely voluntary and you will be given sufficient time to decide whether or not you wish to participate. You are free to decide at all times without giving a reason that you no longer wish to participate in the trial. Withdrawal from the trial will not affect your subsequent treatment or relationship with your treating physician or the hospital staff in any way

**Data protection**
The trial involves the collection of information contained in your medical records and which relate to your disease. It is very important that the information collected is accurate and from time to time it may be checked against your medical records. Duly authorized persons may have access to your medical records. All information will be strictly confidential and your identity will never be divulged; you have the right to access this information at any time.

**Insurance**
Insurance has been taken by the sponsor of the study in accordance with the applicable legislation. If you need to undergo another medical treatment, we advice you to inform the investigator to ensure this will not have any effect on your participation to the trial. Everything has been done and will continue to be done to prevent additional health problems occurring as a result of your taking part in this trial.

**Ethics Committee**
This research protocol has been submitted to an ethics committee whose mission is to verify all conditions for your safety and respect of your rights are respected. Approval to this research has been given by the Ethics Committee of __________________________ on __________________

Contact persons
In case of any problem or question, your doctor will be pleased to answer any further questions and may be contacted as follows:
Name of the doctor: ________________________________
Hospital: _________________________________________
Telephone: ______________________________

If you consent to join this trial, you will be given a telephone number at the hospital that you can contact at any time if you feel unwell or have further questions. Your family doctor will also be told about your taking part in this trial and what is involved, if you agree.
Please take your time to consider this information and do not hesitate to ask further questions of your doctor if anything is not clear. You are entitled to keep a copy of this document after you and your doctor have signed it.

Acceptance of participation
• I have been properly informed of the clinical research that is being proposed to me
• I have received a copy of the patient information sheet
• All my rights have been clearly explained
• I have received a copy of the informed consent document
• I accept to participate in the research entitled Chest irradiation in extensive disease small cell lung cancer
• My participation is completely voluntary and I have the possibility to withdraw my consent at anytime without explanation. This will not affect my relationship with my treating physician.
• The data collected on my behalf will be strictly confidential and treated according to the "Directive on the protection of individuals with regard to the processing of personal data" and the local applicable laws.
• My consent does not discharge the organizers of the research from their responsibilities and I keep all my rights guaranteed by the law”.
• have been informed that the data collected may be used in the future for any scientific purpose while confidentiality will be ensured

Patient's name: ________________________________
Patient's signature: ________________________________ Date: ________________________________
Person designated by the investigator to participate in the informed consent process:
Name: ________________________________
Signature: ________________________________ Date: ________________________________
Investigator's name: ________________________________
Title/Position: ________________________________
Investigator's Signature: ________________________________ Date: ________________________________

This document has been prepared taking into account:
• ICH-GCP Guidelines; Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), Sept. 1997.
• International Ethical Guidelines for Biomedical Research involving Human Subjects, Council for International Organizations of Medical Sciences (CIOMS), Geneva 1993.
Appendix B: WHO performance status scale

Grade Performance scale

0  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 all 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 on any self-care; totally confined to bed or chair.
Appendix C: World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
48th General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician’s knowledge and conscience are dedicated to the fulfillment of this duty.

3. 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."

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

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.
B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate 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.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical 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 consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

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

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.
This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.
Appendix D : Small Cell Cancer VA Classification

**Limited disease:**
The definition of limited disease is based on the possibility of encompassing all detectable tumor within a “tolerable” radiotherapy port. Patients with limited disease have tumor deposits restricted to one hemithorax with regional lymph node metastasis (including ipsilateral, mediastinal and supraclavicular nodes. Ipsilateral superior vena cava syndrome and recurrent laryngeal nerve involvement are also considered as limited disease. Contralateral hilar lymph node are also considered as limited disease.)

**Extensive disease:**
It represents any tumor beyond the bounds defined above (including ipsilateral lung metastases and malignant pleural effusion).