Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

CHARITÉ

Working Group - Gynaecological Oncology (AGO)

and

Working Group Radiological Oncology (ARO)

AGO ARBEITSGEMEINSCHAFT GYNÄKOLOGISCHE ONKOLOGIE E.V.

Deutsche Krebsgesellschaft e.V. aro Arbeitsgemeinschaft Radiologische Onkologie

STUDY PROTOCOL

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on the oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Short Title: Operative Staging prior to Radio-chemotherapy

Sponsored by the Deutsche Krebshilfe
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1. General Information

1.1 Protocol Identification:

Study Number:

Protocol Code:

EudraCT No.: not applicable

Date of Protocol Version: 19/06/2008

1.2 Note on Confidentiality:

The contents of the protocol and test form are confidential and may not be disclosed, either verbally or in writing, to persons not involved without the consent of the study director.

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Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

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Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

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Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Signatures Page **date and signature**

1.4 Unterschriftenseite

PD Dr. med. Simone Marnitz — 14.7.08 Datum

Prof. Dr. med. Christhardt Köhler — 14.07.08 Datum

Prof. Dr. med. Achim Schneider, M.P.H. — 15.07.08 Datum

Prof. Dr. med. Volker Budach — 14.07.08 Datum

Prof. Dr. med. Wolfgang Hinkelbein — 21.07.08 Datum

Prof. Dr. med. Ulrich Keilholz — 25.7.08 Datum

PD Dr. rer. nat. A. Kaufmann — 23.7.08 Datum

Prof. ~~Dr. med~~. Dr. rer. nat. Peter Martus — 25.7.08 Datum

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

1.5 Abstract

The aim of this study is to determine whether the modified therapy on the basis of operative staging and systematic, pelvine and paraaortal lymphadenectomy for patients with cervical carcinomae of the FIGO stages IIB-IV prior to introducing radio-chemotherapy leads to a significant improvement of disease-free survival.

To this end, 250 patients with histologically verified carcinomae of the cervix uteri of the stages IIB-IV shall be randomised to a standard arm (ARM B), whereby the therapy shall be conducted on the basis of the clinical FIGO stage.

The patients randomised to the test arm (Arm A), after determining the clinical FIGO stage, shall initially receive an operative staging in the form of a pelvine paraaortal lymphadenectomy (laparoscopic or open). On the basis of the operatively obtained findings, a ("surgically") modified tumour stage shall be determined. This "surgical" tumour stage, which shall take into account the affection of the lymph nodes, the infiltration of the neighbouring organs and the intraperitoneal spread, shall serve as the basis for the execution of primary, combined radio-chemotherapy. The primary endpoint is the disease-free survival of both groups, the secondary endpoints are overall survival, the local control of both groups, as well as the determination of toxicity and the quality of life.

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1.6 Randomisation Form

Pseudonym

⌊_⌋⌊_⌋ surname Pat.(the last 2 letters)

⌊_⌋⌊_⌋⌊_⌋⌊_⌋ Pat.-year of birth YYYY

Clinic.....

Date of the examinations (dd/mm/yyyy) ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Inclusion and exclusion criteria fulfilled YES ⌊_⌋ NO ⌊_⌋

FIGO **IIB** ⌊_⌋ **IIIA** ⌊_⌋ **IIIB** ⌊_⌋ **IV** ⌊_⌋

Patient information received YES ⌊_⌋ NO ⌊_⌋

Declaration of consent signed YES ⌊_⌋ NO ⌊_⌋

Official stamp

Signature of examining physician _____ Date (dd/mm/yyyy) ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Telephone No. _____ Fax-No. _____

Randomisation result: (shall be issued by the study centre)

Pat.-ID-No ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (shall be issued by the study centre)

Therapy-Arm **A** (Operative Staging): ☐

Therapy-Arm **B** (Clinical Staging): ☐

Randomisation can be carried out between 8 a.m. and 5 p.m. from Mondays to Fridays by Fax using the Randomisation Form.

Fax- No. +49 (030) 84454471

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1.7 Synopsis

Title of the Study	Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy.
Short Study Title	Therapy Optimisation Study for Examining the Influence of Operative Staging
Indication	Cervix carcinoma FIGO IIB-IV
Primary Aim of the Study	Comparison of disease-free survival
Secondary Aims of the Study	Overall Survival Locally recurrence-free survival Acute and late toxicity Quality of life
Study Design	The study is a two-arm, prospective, randomised and multi-centric therapy optimisation trial
Study Population	**Inclusion Criteria;** - Karnofsky-Index =/> 70, - Patients in the age group 18 -70, - histologically verified cervix carcinoma - FIGO stage IIB-IV. - Written Declaration of Consent - Co-operation Capacity of the Patient **Exclusion Criteria:** - Neuroendocrine tumours and/or hybrid types with neuroendocrine components. - Pregnancy, lactation, - Remote metastasis besides paraaortal metastases - Previous malignant diseases - Radiotherapy of the pelvis in the anamnesis Serious, internal, concomitant diseases -Psychiatric diseases that throw doubt on the advisability of participation in the study and after-care, - HIV-Infection and/or AIDS disease, - Drug addiction, - Existing motoric or sensory polyneuropathies > CTC Grade 1

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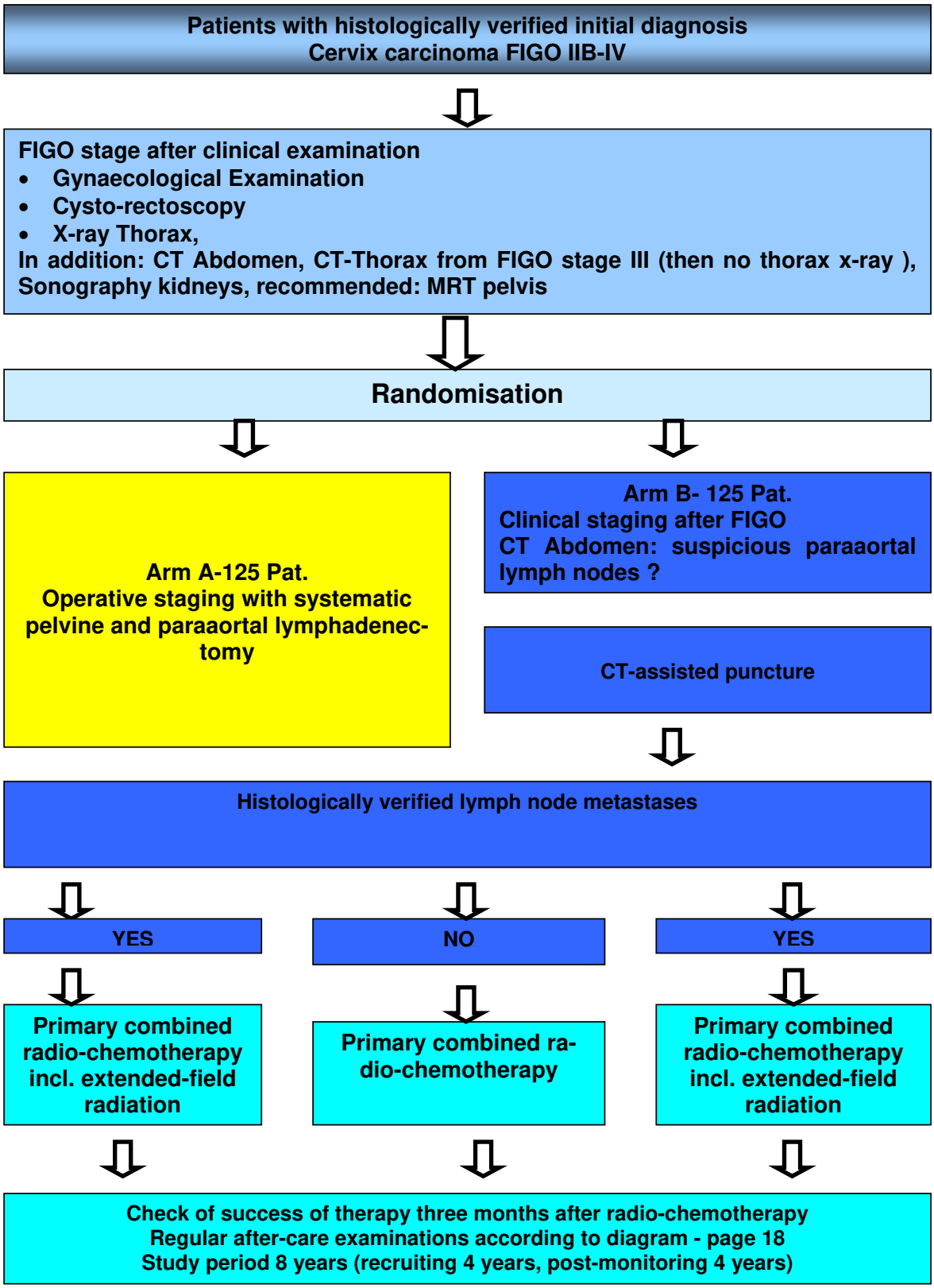
Number of Patients	• 125 patients shall be recruited for each study arm • The primary endpoint is disease-free survival. • Significance testing is carried out with the help of Log Rank Tests (alpha = 0.05 two-sided, beta = 0.20, drop outs 20%),
Therapy	**- Radio-chemotherapy:** Percutaneous 3D-scheduled radiation therapy and afterloading and simultaneous chemotherapy comprising Cisplatin 40 mg/m2 KOF, 1x Weekly, 5 Cycles; in the case of counter-indications against Cisplatin, Carboplatin shall be recommended. In the case of existing paraaortal lymph-node metastases, Extended Field Radiation
Primary Study End Point	The primary study end point is the statistically significant improvement of the disease-free survival of patients after therapy on the basis of the modified tumour stage after operative staging **and** systematic lymphadenectomy prior to radio-chemotherapy in comparison with patients after radio-chemotherapy corresponding to the conventional, clinical FIGO stage.
Secondary Study End Points	Overall Survival Local Control Acute and late toxicity Quality of life, assessed according to EORTC QLQ C-30
Biometry	125 patients shall be recruited for each study arm Significance testing carried out with the help of the Log Rank Test (alpha = 0.05 two-sided, beta = 0.20, Drop outs 20%), Strata: Centre, FIGO Stage
Time Schedule	**Patient-related**: duration of therapy: max. 8 weeks, post-monitoring period: 4 years, estimated termination 2016. Study-related: 2008, recruitment period: 4 years, estimated termination 2016.

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy



1.9 Overview of the Examinations

1.10 Pre-therapeutic Examination

- Comprehensive Anamnesis
- Karnofsky Performance Status
- Gynaecological Examination
- Narcosis examination and abrasio
- Histological verification of the tumour
- X-ray-Thorax at 2 levels, from FIGO stage III CT Thorax, possibly MRT pelvis
- Sonography of the upper abdomen and of the kidneys, alternatively CT Abdomen
- LQ-Questionnaire
- Laboratory:
    - Complete blood count, electrolyte, GOT, GPT, Gamma-GT, tumour marker CEA, CA 12-5 and SCC
- Prior to Planned Radio-chemotherapy:
    - Creatinine-Clearance and audiogram
- Forms 1-5 (see Annex)

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1.11 Post-therapeutic Investigations

*** recommended**

Examinations	After-care examinations after completion of the therapy (months)														
	1.5	3	6	9	12	15	18	24	30	36	42	48	60	72	84
Anamnesis	X	X	X	X	X	X	X	X	X	X	X	X	*	*	*
ECOG	X		X		X		X			X		X			
Gynaecological Examination		X		X	X	X	X		X	X	X	X	*	*	*
(Narcosis examination/ abrasio)*	X		X		X			X				X			
X-ray thorax or CT thorax					X			X				X			
Sonography Upper abdomen and renal /CT			X				X	X	X	X	X	X	X	X	X
(MRT pelvis)	X				X			X		X		X			
Tumour marker	X		X		X		X		X			X			
Toxicity**	X		X		X		X		X			X			
Life quality***		X		X	X			X		X		X			

****After completing the follow-up, routine gynaecological examinations**

*****Forms in the Annex**

Marnitz S, *et al. Int J Gynecol Cancer* 2020; 30:1855–1861. doi: 10.1136/ijgc-2020-001973

2. Rationale / Research Question

2.1 Starting Point

The cervix carcinoma is the second most frequent gynaecological tumour disease worldwide and the third most frequent gynaecological carcinoma In Germany, with an incidence of 12/100 000 (1).

To this day, the classification of the stages of the cervix carcinoma is in accordance with the classification determined by the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) in the year 1947. It is based solely on clinical parameters. (2). Important prognostic factors, such as the affection of pelvine and paraaortal lymph nodes or intraperitoneal seeding, are not reflected in this. The probability of a lymphogenic metastasation grows with the increasing size of the tumour. This amounts to ca. 5% in FIGO stage I, 16% in stage II, 25% in stage III (3).

There exists a close relationship between the number of affected lymph nodes, the frequency of recurrence and the survival rate(4)

Although impermissible for staging according to FIGO, both computer tomography (CT) as well as magnetic resonance tomography (MRT) shall be used in the course of the pre-therapeutic staging. The evaluation of the findings shall be based on morphological criteria in such a manner that lymph nodes affected by tumours, enlarged but not hyperplastic, but not infiltrated lymph nodes, shall be shown as false-negative and/or false-positive. (5). In spite of their widespread use, CT and MRT show insufficient accuracy in detecting pelvine and paraaortal lymph nodes. For CT, the sensitivity in detecting pelvine and paraaortal lymph node metastases from pooled datasets is given as 47% (6, 7) The Inter-group-Study (GOG 183, ACRIN), under every-day conditions, showed for the detection of lymph node metastases a sensitivity of 34% for the CT and 37% for the MRT (8).

The value of FDG-PET/CTs in pre-therapeutic staging of the cervix carcinoma is likewise limited. The same limitations apply in regard to spatial resolution as those that apply for other methods (9) In the case of very small patient populations with various tumour stages, sensitivity to pelvine lymph node metastases is reported between 10% and 72%. (10, 11, 12); for the paraaortal lymph node metastases 58-100% is reported. Also in this case, it is a matter of mixed populations with various stages (13, 14, 15, 16).

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The limitations of clinical staging according to FIGO and of the imaging methods pose the risk of over or under-treatment of the patients.

In view of this, the value of operative staging in the case of cervix carcinoma has been under controversial discussion for decades.

The aim is to determine an exact tumour stage and to adopt an optimal therapy adapted to meet the requirements of the stage of disease of the individual patients. To this end, attention shall be focused on:

1. The affection of pelvine lymph nodes. The therapy concept shall be modified, from the radical operation to combined radio-chemotherapy, depending on the affection of the pelvine lymph nodes. Due to the absence of knowledge regarding the pre-operative status of the lymph nodes and/or false negative findings from the CT and/or MRT and/or PET/CT, many patients are still being subjected to radical hysterectomy. In the case of positive lymph node findings, the indication for adjuvant radio-chemotherapy is then diagnosed. Due to the combination of these two treatment methods, the therapy-related late toxicity is doubled (17). Thus, the aim must be to treat the tumour oncologically with the appropriate modality
2. The affection of paraaortal lymph nodes. Undetected, and therefore untreated, paraaortal lymph node metastases inevitably lead to a progression in this region, even if the tumourous pelvine region is controlled. Histologically verified paraaortal metastases require a concept modification in the form of Extended-Field Radiation. In this way patients without paraaortal affection will not need to undergo prophylactic radiation in this region and patients with verified metastases will receive adequate therapy and the chance of being cured of the disease.
3. Evidence of intra-abdominal seeding poses the need for modifying the intention of the therapeutic concept from curative to palliative, thus saving the patient from having to suffer the unnecessary toxicities of an aggressive therapy.
4. The histological confirmation of infiltration in the neighbouring organs.

The initial works of Piver, Wharton and Delgado on surgical staging documented unacceptably high morbidities and mortalities (18,19 20). This was changed by the use of extra-peritoneal access ports and, quite decisively, by the establishment and standardisation of laparoscopic operation techniques (21, 22, 23, 24, 25). It could be demonstrated that laparoscopic staging leads neither to

an increase in toxicity nor to delaying the radio-chemotherapy (24, 26, 27, 28). Due to evidence of lymph node metastases, therapeutic concepts are modified for 18-45% of the patients,(29, 30, 31, 32, 33). Evidence of improved prognosis for patients after operative staging is yet to be found. The only prospective, randomised study (34) showed for patients after operative staging (open and laparoscopic) and subsequent radio (chemo)therapy a worsened progression-free survival. In the operative staging arm, however, there were more patients with advanced tumours. Due to the premature termination of the study, the primary research question could not be answered. Both in the clinical staging Arm as well as in the operative staging arm the therapy-induced toxicity - ≥ Grade 3 toxicity at 45% and 38%, respectively was unacceptably high. This is attributable to the radiation therapy technique used, which resulted in serious intestinal strain. In contrast to this, it has been demonstrated so far, in ca. 700 patients with nodal positive cervix carcinoma, that the systematic paraaortal and/or pelvine lymphadenectomy with removal of pathologically enlargened lymph nodes significantly improves the prognosis for the patients (26, 27, 35, 36, 37, 38).

2.2 Rationale for the Project

When keeping to the FIGO classification (2),the estimation of the local spread of the tumour is decisively dependent upon the experience of the examiner. It could be shown that for a large proportion of the patients the local tumour stage is underestimated. Moreover, the most important prognostic factor, i.e. the affection of the paraaortal and/or pelvine lymph nodes, is not reflected in the FIGO classification. Hence, many patients are not treated according to their tumour stage.

The available imaging methods (CT,MRT,PET/CT) have limited value in lymph node diagnostics as well as in diagnosing organ infiltration and intra-abdominal seeding. (6, 7, 8, 10, 11, 12, 13, 14, 16). Today, the value of surgical staging for the exact determination of the tumour stage is under dispute . Thanks to the availability of minimal invasive operating methods, it has been possible to considerably lower the morbidity of the pre-therapeutic staging. This refocuses interest in regard to operative staging in gynaecological oncology. It has been verified that, by determining the surgical tumour stage, over-treatment or under-treatment of patients can be avoided and that, in regard to their prognosis, patients benefit from a systematic lymphadenectomy (35, 36, 37). So far, it has not been possible to prove a survival advantage in

prospective, randomised studies. The only randomised study was prematurely terminated (25, 33, 34).

2.3 Rationale for the Treatment and Investigation Methods

These data show the necessity of an exact classification of the stages, taking into account the size of the tumour, the intra-abdominal tumour seeding and the histological affection of the lymph nodes and the neighbouring organs prior to determining the treatment method. To this end, the following patient groups shall be observed:

Group A:

The findings of the operative staging necessitate termination of the planned, radical operation. A primary, combined radio-chemotherapy of the cervix und *pelvine* lymph drainage pathways shall be carried out in the case of histologically free paraaortal lymph nodes.

Group B:

Verified pelvine and/or paraaortal lymph-node metastases necessitate termination of the planned operation. A primary, combined radio-chemotherapy of the cervix und *pelvine and paraaortal* lymph drainage pathways shall be carried out in the case of histological paraaortal lymph node metastases.

Group C:

The findings of the operative staging necessitate the application of the extended field concept due to histologically verified paraaortal lymph-node metastases. Primarily, only radio-chemotherapy of the pelvis was planned in the case that imaging and clinical examination showed no pathological findings in regard to the paraaortal lymph nodes.

For the patients in **Groups A and B** we anticipate no survival advantage. On the other hand, however, we expect a 50% reduction of grave long-term toxicity on the basis of

the data according to Landoni et al (17). However, it is not the aim of this study to substantiate this.

In **Group C** we anticipate no survival advantage. Due to the existing paraaortal lymph-node metastases, these patients would have had no chance of recovery, neither after lymphadenectomy operation nor after only having received pelvic radiation. By increasing the extent of the radiation to include the paraaortal regions and by previously removing the affected lymph-node metastases, these patients were given the chance of being cured. Since the risk of paraaortal affection of the lymph nodes increases with the increase in the FIGO stage, only patients categorised from FIGO IIB shall be included in this study (35, 36, 37).

The aim of this study is to determine whether the therapy of the cervix carcinoma on the basis of operative staging and systematic, pelvine and paraaortal lymphadenectomy shows a significant advantage in regard to disease-free survival for patients with cervical carcinomae. The therapy shall be carried out with equivalent values in both study arms, according to the scientific state of the art, on the basis of the existing guidelines. The treatment schedule can be found in Section 8, the study synopsis on page 15/15 shows an overview of the procedure in the treatment arms. If the therapy of the entity changes during the course of the study period, this shall be adapted to the new standards in the framework of the study.

Since, in the case of this entity, 85% of the recurrences occur during the first two years, a post-monitoring period of four years shall be stipulated. It is estimated that ca. 70 patients can be randomised annually in the study. Should the study objectives be confirmed by the findings, the therapy concept for patients with cervix carcinoma shall be modified accordingly.

3. Study Objectives

3.1 Primary Study End Points

The primary study end point is disease-free survival for patients after therapy on the basis of the modified tumour stage after operative staging **and** a systematic pelvine and paraaortal, infrarenal lymphadenectomy (Arm A) in comparison with patients after therapy according to the clinical FIGO stage (Arm B).

3.2 Secondary Study End Points

Secondary study end points are the local control rate, overall survival. acute and late toxicity and the quality of life after EORTC QLQ C-30 of both therapy arms.

3.3 Scientific Support Programme

Cooperation with other scientists:

Prof. Dr. U. Keilholz, Clinic for Haematology and Oncology, Charité Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin Evaluation of Prognosis Criteria.

PD Dr. A. Kaufmann, Laboratory Director, Research Commissioner of the Laboratory for Tumour Immunology, Hindenburgdamm 30, 12200 Berlin. HPV Diagnostics for cervix carcinoma.

4. Design and Organisation of the Study

Type of Study: therapy optimisation study

Type of Therapy Classification: randomised simple blind

Number and Type of Comparative Groups: 2 parallel groups

Scope of the Study: The study is planned as multicentric. 125 patients shall be included in each therapy arm.

Randomisation Principle: 1: 1

Stratification According to Centre. The operative therapy shall be carried out in centres according to a standardised operative treatment schedule. The radio-chemotherapy is standardised for all centres as stipulated in the study protocol. In addition, it shall be stratified according to FIGO stage.

Time Schedule: the study shall be activated after approval by the Ethics Commission. The Recruiting Phase shall be carried out over a period of 4 years. The post-monitoring period shall be 4 years.

5. Participating Test Centres

A list of the participating centres can be found in the Annex.

6. Selection of Patients

6.1 Inclusion Criteria

- Karnofsky-Index =/> 70
- Patients in the age group 18 -70
- Histologically verified cervix carinoma
  (flat epithelial or adenocarcinoma, adenosquamous carcinoma)
- FIGO stage IIB-IV
- Duly completed and signed, written declaration of consent
- Co-operation capacity of the patient
- adequate renal function prior to radio-chemotherapy (Creatinine Clearance ≥70 ml/h)
- Effective contraception during the radio-chemotherapy
- information and explanation already given to the patient and written declaration of consent

6.2 Exclusion Criteria

- Neuroendocrine tumours and/or hybrid types with neuroendocrine components
- Pregnancy, lactation, women without reliable contraception during the radio-chemotherapy
- Remote metastasis (Exception: histologically verified paraaortal metastases)
- Previous malignant diseases
  (Exception: Lege artis treated basaliomae of the skin)
- Radiotherapy of the pelvis in the anamnesis
- Serious, internal, concomitant diseases
  (myocardial infarction, cardiomyopathy, cardiac insufficiency NYHA III/IV, severe COPD, renal insufficiency, unadjusted diabetes mellitus, uncontrolled infections)
- Psychiatric diseases that throw doubt on the advisability of participation in the study and after-care
- HIV-Infection and/or AIDS disease
- Drug addiction
- Already existing motoric or sensory polyneuropathies > CTC Grade 1

7. Admission, Registration and Randomisation

Patients receive detailed information and explanations in consultation with the investigating physician and/or his deputy before being included in the study. Patients shall receive adequate time for consideration. All questions must be answered and any circumstances that may be unclear to the patient must be clarified. Prior to randomisation, the signed declaration of consent and permission to collect and process person-related data must be obtained. The written consent must be dated and signed independently by the patient.

Consent may be withdrawn by the patient at any time without stating any reasons. The patient shall be made aware that the information relating to the randomisation result will remain in the documentation and that the stored data will be used for further evaluation. Randomisation and registration of the patients shall be carried out centrally by the Institute for Biometry of the Charité (Prof. Martus). Prior to randomisation, a stratification shall be executed according to centre and FIGO stage. Randomisation completed 1:1. This is done by filling out the randomisation form and submitting it by fax (see 7.2).

7.1 Sampling

The additional sampling for the scientific support programme shall be performed after receiving the patients' consent on a separate form. Patients shall receive explanations in regard to the type and number of samples, the sampling mode and the risks involved, as well as the mode, duration and place of the sampling.

7.2 Randomisation

Patients may only be admitted to the study after they have been informed about possible risks and side effects and when they have declared their consent in writing after a consideration period of at least 24 hours. (see form in Annex). Patients must fulfil the randomisation criteria, i.e. there must be neither medical nor other external and/or private reasons that preclude random allocation to the one or the other study arm. For the central randomisation, a computer algorithm is used for dynamic randomisation, which optimises the distribution structure of relevant characteristics in the randomisation groups. This shall be performed after request in the central coordinating centre. The strata are 1. the treatment centre and 2. the

FIGO stages II,III,IV. Randomisation can be carried out between 8 a.m. and 5 p.m. from Mondays to Fridays by Fax using the Randomisation Form.
Fax- No.: +49 (030) 8445 4471

8. Treatment Schedule

8.1 Pre-treatment Diagnostics

During the initial examination, performed by a specialised gynaecologist, the inclusion and exclusion criteria are examined and the resulting findings documented. The following examinations must be performed and/or their results must be available prior to beginning the study:

- Comprehensive Anamnesis
- Karnofsky Performance Status
- Gynaecological Examination
- Narcosis examination and abrasio
- Histological verification of the tumour
- X-ray-Thorax at 2 levels, from FIGO stage III CT Thorax, possibly MRT pelvis
- Sonography of the upper abdomen and of the kidneys, alternatively CT Abdomen
- LQ-Questionnaire
- Laboratory:
    - Complete blood count, electrolyte, GOT, GPT, Gamma-GT, tumour marker CEA, CA 12-5 and SCC, Creatinine Clearance
- Tonal audiogram
- Forms 1-5 (see Annex)

8.2 Systematic pelvine and paraaortal lymphadenectomy

Basically, there are four possible access paths for the operative staging:

1) The laparoscopic transperitoneal
2) The laparoscopic extraperitoneal
3) The open extraperitoneal und
4) The transabdominal transperitoneal access path.

Prior to the lymphadenectomy another narcosis examination should be performed. In particular, the affection of the parametries and/or vagina shall be documented and, if

necessary, histologically proven or excluded. Each centre must ensure that a standard operative procedure is followed within the centre. The systematic operative staging must incorporate the exclusion of intra-abdominal tumour seeding (if necessary biopsies), systematic pelvine and paraaortal lymphadenectomy (LNE) and the operative evaluation of the vesicocervical and rectovaginal septum.

The following procedure is recommended, but can be varied depending on the access path; all suspicious findings in the peritoneum or on the surface of the liver shall be biopsied and examined in the rapid section. After exclusion of an intra-abdominal tumour diffusion, the pelvis minor shall be inspected and the septa vesicocervical/vaginal and rectovaginal biopsied in the case of suspicious findings. Subsequently, a lavage of the the Douglas cavity is performed for a cytological examination. In the case of macroscopically evident affection of the bladder, the rectum or intra-abdominal organs, a biopsy is dispensed with to avoid tumour cell propagation.

The paraaortal lymphadenectomy encompasses the lymph nodes from the iliacal commune vessels to the mouth of the V renalis sinistra in the Vena cava. A biopsy of the lymph nodes in the supraclavicular fossa is performed when the most distant cranial paraaortal lymph nodes are affected.

Pelvin iliacal external, inter-iliacal and obturator lymph nodes subsequent to the paraaortal lymph nodes shall be removed. A sufficient number of removed lymph nodes (paraaortal ≥ 10, pelvin ≥ 15) shall be guaranteed by selection of various operative techniques.

8.3 Therapy

Patients initially diagnosed with a cervix carcinoma FIGO stage IIB to IV shall be included in the study. After appropriate diagnosis, the FIGO stage shall be determined. Subsequently the patients shall be randomised to one of the two study arms (Arm A or B).

8.3.1 Therapy in Arm A

The patients included in the first arm (Arm A) shall undergo operative staging, including systematic pelvine and paraaortal lymphadenectomy. The determination of the modified tumour stage of these patients shall be performed by evaluating the histological findings of the lymph node staging and the removed biopsies and the lavage. The modified tumour stage can be seen from additional information through the op

erative staging, e,g, histologically verified affection of the lymph nodes paraaortal (pM1 LYM) and/or pelvine affection of the lymph nodes (pN1), which then show the indication for radio chemotherapy, histologically verified bladder affection with cystoscopic pathological findings for the bladder, which must be classified as stage IVA, or a positive peritoneal cytology, which signifies remote metastasis and means changing the intention of the therapy from curative to palliative.

8.3.2 Therapy in Arm B

Here no operative staging is conducted and the therapy is performed in accordance with the currently valid guidelines of the DGGG depending on the primary, clinically determined tumour stage (FIGO). After completing the necessary diagnosis, (Section 8.1) the patients undergo either primary operation or radiotherapy, depending on the FIGO stage. In the event of existing risk factors, the patients having undergone primary operation shall receive adjuvant radio-chemotherapy according to the currently valid guideline.

The exception to this applies to those patients for whom the abdomen CT reveals a suspected paraaortal affection of the lymph nodes. These patients must undergo histological verification of the lymph node affection by means of a CT-assisted puncture. In the case of histologically verified affection of the paraaortal lymph nodes, radio-chemotherapy is indicated under exclusion of the paraaortal region. Patients in FIGO stage IVA with histologically verified affection of the bladder and/or rectum and/or positive samples from the septum vesicouterinum and/or fistula formation shall be informed about the possible therapy options of the primary exenteration versus primary radio-chemotherapy. An interdisciplinary decision in regard to the therapy shall be made together with the patient.

8.3.3 Chemoradiation

Combined percutaneous radiation by means of afterloading shall be carried out. Simultaneously, a chemotherapy with Cisplatin shall be applied. In the case of counter-indications against Cisplatin, Carboplatin shall be used.

8.3.3.1 Percutaneous Radiation

The primary radio-chemotherapy should be performed at the latest within four weeks after completion of the staging. A minimum time interval to be observed is not defined.

The percutaneous radiation therapy shall be conducted as 3D-scheduled radiation therapy in multi-field technique on a linear accelerator. The patients shall be radiated conventionally and fractioned in prone or dorsal position under inclusion of the primary tumour region and the pelvine lymph drainage paths (iliacal common to L4/5, internal, external, interiliacal, presacral to S2/3). The single dosage shall be 1.8 Gy, 5 fractions weekly, up to a dosage of 50.4 Gy. The percutaneous radiation treatment must be combined in each case with the brachytherapy. The overall dosage on the macroscopic tumour should not exceed 80 Gy (BED_{2Gy}). For clinically certain and/or histologically verified affection of the parametrium, an increase in the local dosage for this region up to 54 Gy - 59.4 Gy is recommended. Maximum protection of the rectosigmoid and all the bladder must be ensured (39, 40). The use of the Brachytherapy is also unacceptable according to the recommendations of the GEC-ESTRO Group (41).Before beginning the radiation therapy, all radiation fields must be verified; in the case of good field position the documentation of all fields must be guaranteed once weekly.

8.3.3.2 „Extended Field"- Radiation

In the case of histologically verified paraaortal metastases, radiation of the paraaortal lymph node region is recommended. This should be conducted as 3D-scheduled radiation, with particular observation of the renal tolerance, using a conventional fractioning of 5 single weekly dosages of 1.8 Gy up to a total dosage of 50.4 Gy in the case of macroscopic lymph nodes, but removed in the framework of the systematic lymphadenectomy. In the case of tumourrest (e.g. after corresponding clip marking) a small-volume boost should be applied to this region.

8.3.3.3 Afterloading

In every case, the therapy of the cervix carcinoma should include, as an integral component, the afterloading therapy. The afterloading should be conducted with single dosages, each of 5 Gy, once to twice a week enveloping the tumour up to a total dosage of 25-30 Gy. The total dosage, including the percutaneous therapy and the afterloading should not be lower than 80 Gy in the region of the primary tumour (39, 40, 41)

No percutaneous radiation therapy and no simultaneous chemotherapy should be conducted on the afterloading days. The beginning of the afterloading therapy shall be adjusted to the local findings; in the case of small tumours, afterloading can begin in the first week of therapy. In the case of larger tumours, the afterloading will be applied later, e.g. as from the third week of therapy, in order to exploit the involution of the tumour.

In the case of locally advanced tumours, the number of afterloading applications can be adjusted to the clinical circumstances. In the event of a clinically certain and/or histologically verified affection of the vagina, the target volume for the afterloading shall be adapted accordingly. For distal affection of the vagina, the inguinal region should be checked for affection (e.g. sonography, MRT).

Therapy interruptions for equipment maintenance, holidays must be compensated in such a manner that the total duration of the therapy amounts to < 56 days (39, 40).

8.3.3.4 Simultaneous Chemotherapy

The application of a simultaneous chemotherapy is an integral component of the curative therapy concept. This shall be performed with Cisplatin 40 mg /qm KOF 1x/weekly up to a cumulative dosage of 200 mg/qm KOF, respectively. In the case of counter-indications against Cisplatin, Carboplatin shall be used. Details regarding dosage and execution are described in section 21.5.

8.3.3.5 Intermediate tests during the radio-chemotherapy

During the therapy, the patients undergo clinical monitoring and chemical monitoring in the laboratory and documentation of the acute toxicity is carried out (Forms 10 and 12 see annex).

8.3.3.6 Supportive measures during the radiation therapy

Supportive measures normally used in the clinic should be carried out depending on the condition of the patient. No special recommendations are given.

8.3.3.7 Documentation of radiogenic side effects

The documentation of acute radiogenic reactions shall be carried out according to the CTC 3.0 Score and the late radiogenic side-effects according to the LENT-SOMA Scaling System. The recording of the acute reactions shall be performed once per

week during the radiation therapy and those of the late side-effects at every follow-up examination (Forms 10, 12 and 15 see annex). See also the tabular overview of the follow-up examinations on page 18.

8.3.4 Follow Up

Scope and time intervals of the follow-up examinations are shown in the overview on page 18. Interdisciplinary aftercare provided by radiation therapists and gynaecological oncologists is recommended.

8.3.5 Salvage Therapy

The therapy to be applied in the case of persisting tumours after radio-chemotherapy and/or in the event of recurrence is an individual, interdisciplinary decision, which should be reached accordingly. Prior to initiating palliative therapies, the indication in regard to secondary hysterectomy and/or exenteration shall be checked.

9. Clinical Studies

9.1 Admission and Inclusion Tests

The necessary examinations are described under 8.

9.2 Longitudinal Studies

The longitudinal studies are described in the overview on page 18 Interdisciplinary aftercare provided by radiation therapists and gynaecological oncologists is recommended.

10. Study Pathology

The following factors shall be established:

1. The tumour type according to WHO classification and a standardised tumour grading
2. The localisation and the number of the removed as well as the affected lymph nodes, separately for the pelvine and paraaortal lymph node areas, respectively, as well as evidence of extrascapular growth.
3. Haemangio-invasion, lymphatic vessel invasion
4. HPV-Status

The consultant pathologist of the study is Prof. Dr. Th. Löning, Albertinenpathologie, Fangdieckstr. 75 A, 22547 Hamburg.

11. Study Participation Period

Participation in the study comprises the follow-up examinations shown on page 18. According to the study profile, the follow-up examinations shall be continued over a period of 4 years. Changing study arms is not possible. A premature termination of the protocol therapy in the case of individual patients may take place for the following reasons: unacceptable toxicity, an intercurrent disease or other reasons which, in the view of the attending physician, are detrimental to the evaluation of the clinical status to a significant extent, as well as the wish of the patient to terminate the therapy. The patients shall have the right to withdraw their consent to participating in the study at

any time without stating reasons. For further details, see the chapter on biometry and statistics.

If the study therapy should be rejected after randomisation, the patient shall receive the standard therapy on the basis of the current guidelines. In the event that a patient should prematurely terminate the therapy (radio-chemotherapy), subsequent therapies shall be at the discretion of the fellow attending physicians.

12. Recording the Therapeutic Effectiveness

Patients undergoing radio-chemotherapy shall receive clinical examinations and imaging tests as determined in the post-therapeutic schedule. For the evaluation of the pathological remission, a narcosis examination and abrasio 3 months after completion of the treatment is recommended. If the examination should show conclusive proof of a vital tumour, a decision must be made in regard to secondary hysterectomy on the basis of jointly reviewing the findings of the MRT, the histological examination, the clinical findings and, if necessary, the tumour marker. In the case of no pathological findings, the follow-up examinations shall take place (schedule on page 18).

13. Determining Safety

13.1 The Recording and Evaluation of Undesirable Events

Radiochemotherapy-associated acute toxicity encompasses all events within 90 days after the beginning of the radio-chemotherapy. Late toxicity includes all events that occur on the 91st day after the beginning of the radio-chemotherapy or later. The evaluation is conducted on the basis of the CTC 3.0 and/or the LENT-SOMA criteria (See annex).

Every undesirable event shall be documented regardless of whether there is a causal relationship with the study therapy.

The examiner shall report every serious or unexpected, undesirable event within 24 hours to **Fax No. 030- 450 562 972.** In the case of mortalities, the autopsy report shall be submitted later.

The examiners and test centres taking part in the study shall be informed at three monthly intervals by the manager of the clinical study concerning all events reported.

Unexpected, hitherto unknown, effects for which a causal relationship with the study medication cannot be excluded shall be reported to the study participants within one week. The legally regulated reporting of the side-effects of pharmaceuticals to the responsible authorities shall be carried out by the study directors. If, at an early point, there is a frequent occurrence in one or both of the study arms of events (grade 4 and 5 toxicity), the study safety board shall be commissioned to analyse the undesirable events and to make a decision regarding the consequences, including modification of the trial schedule or, if necessary, a possible termination of the study. Frequent occurrence shall be defined when the toxicity grade 4/5 according to at least 100 patients is higher than 15%.

13.2 Recording and Evaluating Toxicity and Life Quality

Time Points: the systematic evaluation of toxicity shall be carried out before the beginning of the treatment and weekly during the treatment (See annex, Form 12) and, in the further course, in accordance with the schedule on page 18.

13.2.1 Evaluation Criteria :

The evaluation is conducted on the basis of the CTC 3.0 and/or the LENT-SOMA criteria.

13.2.2 Life Quality - EORTC Questionnaire

Life quality shall be recorded before the beginning of the treatment and in the further course of the study (3 months, 6 months, 1 year and then every 6 months), using the standardised questionnaire (See annex 20.8).

This questionnaire for the evaluation of life quality (42) consists of 30 single items which described the multi-dimensional construct "life quality". The questionnaire is valid and reliable and is well accepted by the patients in clinical studies. It presents no great strain on the patients in terms of emotion or time. After evaluation of the factors analysis, the individual items provide information in regard to the following scales: functional status, ability to work, general symptoms, such as fatigue, nausea, pain, shortness of breath, sleeping disorders, lack of appetite, gastrointestinal symptoms and, in addition, cognitive, emotional, social and financial strains, physical condition, treatment strain, confidence and hope.

13.2.3 Safety Monitoring:

The Safety Board shall regularly monitor the collected data in regard to safety. Meetings once annually are planned.

14. Study Duration / Study Termination

The conditions for the inclusion of the last patient and the termination of the post-monitoring period is determined by a defined number of patients included. The study is planned to begin in 2008. With a four-year recruitment phase and a four-year post-monitoring period, the duration amounts to 8 years.

The study shall be abandoned if, during the recruitment period, another therapy option should become available with significantly improved therapy success. Should the number of patients recruited in the first 2 years be <25% than the total target number, the study group shall recommend that the study be abandoned. If, at an early point, there is a frequent occurrence in one or both of the study arms of events (grade 4 and 5 toxicity), the study safety board shall be commissioned to make a decision regarding a possible termination of the study. Frequent occurrence shall be defined when the toxicity grade 4/5 according to at least 100 patients is higher than 15%.

The decision to abandon the study shall be made by the safety board.

15. Biometry

15.1 Basis for Estimating Effects

In the therapy of the cervix carcinoma, there exist, apart from studies, the following therapy options, verified and backed by the current guideline (43).

1. **Exclusive Operation**
2. **Exclusive Radio-Chemotherapy** under inclusion of the primary tumour region and the pelvine lymph drainage pathways
3. **Exclusive radio-chemotherapy** under inclusion of the primary tumour region, the pelvine **AND the paraaortal lymph drainage pathways**
4. Radical **Operation followed by adjuvant Radio(chemo)therapy** under inclusion of the primary tumour region and the pelvine lymph drainage pathways (In the case of risk factors)

5. Radical **Operation** followed by adjuvant Radio(chemo)therapy under inclusion of the primary tumour region, the pelvine lymph drainage pathways (In the case of risk factors) AND/OR the **paraaortal lymph drainage pathways** in the case of intra-operatively verified paraaortal lymph node metastases

The first three options are planned, whereas 4 and 5 are derived from the histological processing of the operation compound.

As a result of the preoperative staging, the following modifications of the therapy may occur:

A The planned exclusive operation will be abandoned and, in its place, a primary radio-chemotherapy (tumour region and pelvine lymph drainage pathways) will be carried out.

B The planned exclusive operation will be abandoned and, in its place, a primary radio-chemotherapy (tumour region **AND** paraaortal lymph drainage pathways) will be carried out.

C The primary, combined radio-chemotherapy (tumour region and pelvine lymph drainage pathways) will be extended to include the paraaortal region (Extended Field due to paraaortal lymph node metastases verified during preoperative staging).

To **Group A**/**B** belong those patients who clinically had no affection of the lymph nodes (neither pelvine nor paraaortal), who are allotted to the FIGO stage IB and IIA and who, on the basis of the operative staging, were classified with a higher tumour stage (local and/or lymph node affection).

To **Group C** belong the patients between FIGO stage IIB and IV without clinical affection of the paraaortal lymph nodes, independent of the pelvine lymph node status. The proportion of patients with paraaortal metastases in this sub-group (IIB-IVA FIGO) is assumed to be 30%.

The **Group A**/**B** is not relevant to the study.

In **Group C** we anticipate a survival advantage**.** Patients with recorded paraaortal and untreated metastases all die of their tumour disease. In contrast, patients with verified ones, after systematic lymphadenectomy and radio-chemotherapy have an expected 5-DFS 50% vs 0% (e.g. 1% in nquery, 35, 36, 38,). The 70% of the patients without upstaging have a DFS of ca 50% in both arms (26, 27).

15.2 Case Rate Estimate

For this reason, the case rate estimate shall be confined to patients allocated to **Group C**, i.e. to patients with FIGO stage IIB to IV, who, per se, show an indication for radio-chemotherapy and who bear the highest risk for an upstaging. This group comprises patients with a 30% risk for paraaortal lymph-node affection. We estimate that, for 30% of these patients, the operative staging and the systematic lymphadenectomy will result in an upstaging (Effect 1). For all patients, it may be assumed that the systematic lymphadenectomy and the resulting reduction in the size of the tumour mass gives rise to a higher probability of tumour eradication (Effect 2).

Effect 1: We assume that in the case of patients with verified paraaortal affection (30% of the total patients) a 40% disease-free survival after five years can be achieved. For these patients, if no operative staging is carried out, a five-year survival of 5% at the maximum is to be expected (27, 38). Effect 1 is irrelevant for patients without upstaging.

Effect 2: Effect 2 is relevant only for those 70% of the patients who did not undergo upstaging. On the basis of the work of Fletcher et al. (44) we estimate that, as a result of the systematic lymphadenectomy and the reduction in the number of clonogenic tumour cells, a five-year survival of 60% could be achieved, and that without systematic lymphadenectomy, a five-year disease-free survival of 50% would be achievable.

Although Effect 2 could likewise take effect on patients after upstaging, due to the low survival probability of the subgroup with not recognized and not resected paraaortal metastases, this effect, however, shall be neglected.

Hence, in total, we estimate the following:

Therapy/Result	5-Y DFS	with op. staging	without op. staging
Upstaging	30% (rate)	40%	5%
No upstaging	70% (rate)	60%	50%
Total	**100%**	54%	36.5%

This results in an expectable difference in the 5-year disease-free survival of 17.5% (54% with surgical staging and 36.5% without surgical staging) Under normal statistical planning conditions (Error 1. Type = 5%, two-sided,Error 2. Type = 80%), with the help of the software Nquery (release 5.0), this results in 100 evaluable patients with a total of 129 events per group. With an estimated 20% of drop-outs, 125 patients per group, i.e. a total of 250 patients, must be recruited. The database shall be closed after observation of the 129th event. Events This is then followed by the statistical analysis.

15.3 Rationale for Limiting the Spectrum of Patients

The probability for the early stages IB2 and IIA of paraaortal affection of the lymph nodes amounts to a maximum of 10-15%. Hence, the benefit in regard to upstaging (Effect 2) and subsequent survival in relation to the group as a whole is relatively small and would probably result in a survival advantage of ca. 4% to 6%. Although with an end point combining toxicity and survival a further advantage of about 1% - 2% could also be expected. All in all, however, the strength of the effect would be insufficient to enable this patient group to achieve the necessary power. The early stages IB2 and IIA make up (27) ca. 25% of the total population and therefore, due to the small expectable effect, would prolong the study period. However, the prospect of not including a comparative record of these patients in the framework of the study documentation shall be taken into consideration.

15.4 Statistical Evaluation

15.4.1 Zero Hypothesis

The disease-free survival of patients after treatment according to the clinical FIGO stage is equally high as for patients treated after the modified tumour stage.

15.4.2 Alternative Hypothesis

The disease-free survival of patients after treatment according to the modified tumour stage is longer than after treatment according to the clinical FIGO stage.

15.4.3 Definition of Evaluation Population

The primary evaluation population is the Intent-to-Treat Population. Patients who withdraw from the study, immediately after randomisation, i.e. before gathering further findings, are classified as not evaluable for the Intent-to-Treat Population. Patients who refuse further participation only in the course of the diagnosis or therapy, but who consent to the use of their data shall be analysed in the Intent-to-Treat Population.

The secondary evaluation population is the Per-Protocol Population. The decision as to whether a patient should belong to the Intent-to-Treat or to the Per-protocol Population depends on the diagnosis and therapy conducted and the documentation of the aftercare. The evaluation of the execution of the therapy and aftercare shall be carried out blind in relation to the study arm. This is not possible for the evaluation of the diagnosis conducted.

However, in the intent-to-treat population, safety will be analysed in relation to the actually conducted diagnosis and therapy ("as treated").

15.4.4 Planning of the Confirmative, Statistical Evaluation

The primary analysis shall be carried out by means of a two-sided LogRank Test for disease-free survival. A sensitivity analysis shall be carried out in that the primary analysis shall be stratified for the tumour histology factors (squamous or adenocarcinoma), tumour stage (Figo IIB, Figo IIIA, Figo IIIB, Figo IV), lymph node status (positive/negative) in a Cox Proportional Hazard Model. All other bowdlerised variables (time to local recurrence, time to local recurrence *or* metastasis, time to late toxicity) shall likewise be compared with the LogRank Test The other variables shall be compared between the study arms in accordance with their scaling with the help of the Chi-Quadrat-Test, the Mann-Whitney rank-sum test or the t-Test. The examination of the normal distribution shall be performed according to the criterion “Inclination between -1 and +1“ in relation to the pooled deviations to those

for the mean group values. Exploratively, all variables examined with the help of the t-Test shall also be calculated with the Mann-Whitney Test.

Likewise exploratively, prognosis factors shall be examined with the help of multiple regression models (Cox-Regression (bowdlerised data), logistical regression (binary data), proportional odds model (ordinal data) or linear regression (constant data). As secondary analysis, a comparison shall be performed, with the help of the Cox-Model, of the study arms adjusted for the stratification criteria and relevant prognosis factors. Likewise exploratively, interactions between the study arm and the prognosis factors shall be examined. The description of the data shall be executed on the basis of the tables, parameters and graphics according to the scaling level and the respective variables. For all analyses, a two-sided significance level of 0.05 shall be determined. Only the primary analysis is confirmatory. All other significances that found shall be interpreted as non-confirmatory. The analysis shall begin after the documentation of the 129th event.

15.4.5 Blinding

As far as possible, the evaluation of the effectiveness and safety in the course of the study should be blinded.

15.4.6 Dealing with Missing Values

A comparison of the frequency of missing values shall be carried out between the two study arms. In the case of equal frequency of the missing values, the locf-Method (least observation carried forward) can be used for the secondary target criteria.

15.4.7 Presentation of the Findings

The presentation of the findings shall be performed according to:

The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. The Lancet 2001; 357:1191-94.

15.4.8 Tasks of the Biometry

The tasks of the biometry during the study period are defined as follows:

- Co-operation on the structure and programming of the database.
- Participation in the creation of standardised database queries.
- The execution of the randomisation.

- Intermediate evaluation for checking the data quality (correction of individual values, checking distribution discrepancies between study centres,Identification of off-scale/extreme values, completeness of the CRFs/entries in CRFs, multi-dimensional plausibility tests).
- Preparation of the data monitoring at study meetings.
- Participation in the further development of standardised database queries.
- Continual further development of an automated reporting system with the aim of detecting temporal trends and systemic differences between the centres.
- The preparation of evaluations and presentations for study meetings.
- The creation of a detailed statistical analysis plan (SAP).
- The modelling of the relevant co-variables for baseline adjustment.
- The creation of evaluation routines/macros for statistical evaluation, including the preparation of data presentations (e.g. the creation of model tables).
- The preparation of the Blind Review for the efficient classification of patients in the study population.

The verification of the data shall be carried out in the framework of study meetings on the basis of the data prepared by the biometry. In doubtful cases. the medical health records shall be examined in advance by the study management together with the participating centres in the framework of a part of the study meetings.

16. Data Management

16.1 Patient Identification List

Or patient related data shall be recorded in pseudonymised form- Patient identification numbers shall be created with five digits, two digits representing the centre, 3 digits representing the patient. The patient identification list with the full names of the patients and the identification numbers shall be kept by the study director. The patient identification list shall be archived for 10 years.

16.2 Data Collection/Documentation Form

Data collection shall be executed concurrently, checked by the study director and recorded with ballpoint pen.

16.3 Data Processing

The data recording shall be executed with the help of an ACCESS database. For statistical analysis, the statistical data shall be read into SPSS and SAS.

The biometric centre shall submit internal, intermediate reports to the study management. These reports shall not have the character of planned intermediate analyses, with the possibility of the premature termination of the study, or of an adaptive design adjustment, with the exception of the abandonment of the study for security reasons on the basis of the vote of the Safety Board. At study meetings, the presentation shall merely contain overall analyses without subdivision according to study arm.

16.4 Paper-based Data Management

The data shall be recorded in an electronic database (ACCESS) in the central office of the study. The data shall be entered by two persons independently of one another (double data entry). The examination of the correctness of the data shall be performed by ranking, validity and consistency checks. Implausible or missing data can be corrected and/or completed (query management). The queries must be executed in writing and shall be stored together with the test forms. Every amendment to the data, e.g. due to the entering of answered queries, shall be documented in the databank by means of automatic amendment tracking (Audit Trail).

At the end of the study, after the entry of all data, the database shall be closed.

This procedure shall be documented.

16.5 Safekeeping of the Study Documents

After completion of the final report, the originals of all central study documents shall be archived at the respective participating centre for at least 10 years.

The original data of the study patients (medical health records) shall also be archived for 10 years. Documentation in regard to radiation treatment shall be archived in accordance with legal regulations for 30 years.

16.6 Data Protection

On the basis of a security concept, it shall be ensured, among other things, that data is protected against unauthorised access and data loss and that the provisions contained in the Data Protection Act are adhered to. The study data is subject to protection against third party access and shall only be accessible to members of the study team. These members shall be bound to secrecy. In the event that a patient withdraws consent, it shall be ascertained to what extent the stored data is still needed. No longer needed data shall be immediately erased.

17. Quality Assurance

17.1 Data Safety Monitoring Board

Members - see page 10

17.2 Standardisation and Validation

The measuring methods and evaluation criteria shall be standardised as far as possible in all participating centres.

17.3 Controlling the Course of the Study and the Quality of the Data

See section 15.4.8

18. Ethical Principles

Ethics Commission This study protocol shall be presented to the competent ethics commission concerned. All centres involved shall likewise apply for the approval of the responsible ethics commission.

In the event of amendments to the protocol, the responsible ethics commission shall be informed.

Information for the Patients

Every patient shall receive precise information in regard to the study, the randomisation procedure and participation.

Consent to Participation in the Study

Every patient shall submit a written declaration of consent to participating in the study. The patients shall receive sufficient time to clarify any unanswered questions and make a decision before any measures are introduced for their participation in the study. A model patient information sheet and declaration of consent are enclosed in the annex.

The Usage, Storage and Disclosure of Data

Patients shall be informed about the pseudonymised disclosure and usage of their data for the purpose of scientific evaluation.

19. Legal and Administrative Regulations

19.1 GCP

The recommendations of Good Clinical Practice shall be observed (J Clin Oncol. 2008;26:2562-7).

19.2 Legal Principles (German Pharmaceuticals Act, National Regulations)

The legal provisions of the Radiation Protection Ordinance (Federal Gazette 2001 Part I No. 38, dated 26.7.2001), of the X-ray Ordinance and the Radiation Protection Directives shall be adhered to.

19.3 Patient Insurance

This clinical study is covered by insurance protection provided by the Feuersozietät-Betriebs-Haftpflicht-Versicherung (operational liability insurance) No. 2222-016.925.716 of the Charité (see annex). All at the test centre is must check their insurance status via their liability insurance and obtain written confirmation.

19.4 Funding

The study is sponsored by the German Cancer Aid (Deutsche Krebshilfe).

19.5 Final Report and Publication

After completion of the biometric evaluation, an integrated report shall be prepared by the study of management. The report shall contain the clinical report, the statistical

report, tables of individual values and the final conclusion. It shall be signed by the study directors (biometricans).

The publication of the findings shall take place independent of the findings of the study.

19.6 Adherence to the Protocol and Protocol Amendments

The study protocol shall be strictly adhered to. Every deviation from the envisaged examination and treatment measures or time schedule under the responsibility of examiner shall be documented, giving reasons.

Modifications or additions to the study protocol may only be initiated and authorised by the study management and the safety board.

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

20. Table of Annexes

20.1 Model Documentation Forms

20.2 Model Patient Information and Declaration of Consent

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21. Literature

Marnitz S, *et al. Int J Gynecol Cancer* 2020; 30:1855–1861. doi: 10.1136/ijgc-2020-001973

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

20.1 Model Documentation Forms

Form 1- Paraclinic

Pat.-ID-No ⌊_____⌋
shall be issued by the study centre

Pseudonym
⌊___⌋ surname Pat.(the last 2 letters)
⌊____⌋ Pat.-year of birth YYYY

LABORATORY TESTS Date of blood sample (dd/mm/yyyy) ⌊_____⌋

Leukocytes (/nl) ⌊____⌋

Absolute Neutrophil Count (%) ⌊____⌋

Thrombocytes (/nl) ⌊____⌋

Haemoglobin (g/dl) ⌊____⌋

Creatinine (mg/dl) ⌊____⌋

Creatinine Clearance (ml/min) ⌊____⌋

GOT (U/l) ⌊____⌋

GPT (U/l) ⌊____⌋

Sodium (mmol/l) ⌊____⌋

Potassium (mmol/l) ⌊____⌋

Abnormal Blood Count Values _____

SCC ⌊____⌋

CA 125 ⌊____⌋

CEA ⌊____⌋

_____
Signature of examining physician Date (dd/mm/yyyy) ⌊_____⌋

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 2- Anamnesis

Pat.-ID-No	Pseudonym	
⌊_⌊_⌊_⌊_⌊_⌊_⌋	⌊_⌊_⌋	⌊_⌊_⌊_⌊_⌋
shall be issued by the study centre	surname Pat.(the last 2 letters)	Pat.-year of birth YYYY

Anamnesis (Date) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ (dd/mm/yyyy)

Karnofsky Status ⌊_⌊_⌊_⌋ % ECOG (0-4) ⌊_⌋

Age (years) ⌊_⌊_⌋

Height (cm) ⌊_⌊_⌊_⌋

Weight (kg) ⌊_⌊_⌊_⌋

Nicotine (py) ⌊_⌊_⌋

Additional Diagnoses

Cardiovascular diseases ⌊_⌋ Yes ⌊_⌋ No

Diabetes mellitus ⌊_⌋ Yes ⌊_⌋ No

Pelvis Operations ⌊_⌋ Yes ⌊_⌋ No

Previous radiation therapy ⌊_⌋ Yes ⌊_⌋ No

Previous Chemotherapy ⌊_⌋ Yes ⌊_⌋ No

Menopause Status

Premenopausal ⌊_⌋ Postmenopausal ⌊_⌋

Gravidity Number ⌊_⌋ Parity Number ⌊_⌋

Signature of examining physician Date (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 3- Histology

Pat.-ID-No ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ shall be issued by the study centre

Pseudonym ⌊_⌊_⌋ surname Pat.(the last 2 letters) ⌊_⌊_⌊_⌊_⌋ Pat.-year of birth YYYY

Date of the examination ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ (dd/mm/yyyy)

Biopsy: Yes ⌊_⌋ No ⌊_⌋ Not Evaluable ⌊_⌋

Histology: ⌊_⌋ squamous cell carcinoma

⌊_⌋ Adenocarcinoma

⌊_⌋ Adenosquamous Carcinoma

Grading: ⌊_⌋

Lymphatic Vessel Invasion: ⌊_⌋ L0 ⌊_⌋ L1

Vessel Invasion: ⌊_⌋ V0 ⌊_⌋ V1

Size of Tumour: ⌊_⌋ < 4cm ⌊_⌋ > 4cm

HPV-Status: ⌊_⌋ pos. ⌊_⌋ neg. ⌊_⌋ unknown

Signature of examining physician Date (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 4- Tumour Stage

Pat.-ID-No

|_|_|_|_|_|_|_|

shall be issued by the study centre

Pseudonym

|_|_| surname Pat.(the last 2 letters)

|_|_|_|_| Pat.-year of birth YYYY

Date of the examination |_|_|_|_|_|_|_|_| (dd/mm/yyyy)

Tumour stage according to FIGO according to the clinical examination:

Clinical FIGO _____

Tumour stage under consideration of the operative staging:

Corrected stage after staging _____

Please enter the exact LC number (Ex.: T2a pN1(3/16 pelv; 0/10 paraaortal) M0).

_____

Signature of examining physician Date (dd/mm/yyyy) |_|_|_|_|_|_|_|_|

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 5- Imaging

Pat.-ID-No ⌊_⌊_⌊_⌊_⌊_⌊_⌋ shall be issued by the study centre

Pseudonym ⌊_⌊_⌋ surname Pat.(the last 2 letters) ⌊_⌊_⌊_⌊_⌋ Pat.-year of birth YYYY

Date of the examination ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ (dd/mm/yyyy)

Type of Imaging
- ⌊_⌋ CT
- ⌊_⌋ MRT
- ⌊_⌋ Other: _____

Size of Tumour after MRT ⌊_⌊_⌊_⌋ cm x ⌊_⌊_⌊_⌋ cm

Pelvine lymph nodes in the imaging:
- ⌊_⌋ not enlarged
- ⌊_⌋ enlarged, but smaller than 1.5cm, Number: ⌊_⌊_⌋
- ⌊_⌋ enlarged, larger than 1.5cm, Number: ⌊_⌊_⌋
- ⌊_⌋ not usable

Paraaortal lymph nodes in the imaging:
- ⌊_⌋ not enlarged
- ⌊_⌋ enlarged, but smaller than 1.5cm, Number: ⌊_⌊_⌋
- ⌊_⌋ enlarged, larger than 1.5cm, Number: ⌊_⌊_⌋
- ⌊_⌋ not usable

X-ray-Thorax no pathological findings ⌊_⌋ pathological findings ⌊_⌋

Sonography no pathological findings ⌊_⌋ pathological findings ⌊_⌋

_____

Signature of examining physician Date (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Marnitz S, *et al. Int J Gynecol Cancer* 2020; 30:1855–1861. doi: 10.1136/ijgc-2020-001973

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 6- Operation

Pat.-ID-No	Pseudonym	
⌊_⌊_⌊_⌊_⌊_⌊_⌋	⌊_⌊_⌋	⌊_⌊_⌊_⌊_⌋
shall be issued by the study centre	surname Pat.(the last 2 letters)	Pat.-year of birth YYYY

Operation:

Date: (ddmmyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌋

⌊_⌋ Pelvine lymphadenectomy

⌊_⌋ Paraaortal lymphadenectomy

⌊_⌋ laparoscopic extraperitoneal

⌊_⌋ laparoscopic transperitoneal

⌊_⌋ Open abdominal access path

⌊_⌋ Open extraperitoneal access path

⌊_⌋ No Operation

⌊_⌋ Conversion Laparoscopy- Laparotomy. Reason:

Signature of examining physician Date (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌋

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 7- Operative Complications

Pat.-ID-No	**Pseudonym**	
⌊_⌊_⌊_⌊_⌊_⌊_⌋	⌊_⌊_⌋	⌊_⌊_⌊_⌊_⌋
shall be issued by the study centre	surname Pat.(the last 2 letters)	Pat.-year of birth YYYY

Early (d 0-9) and late (d10 and later) operation-associated complications

⌊_⌋ Thromboemboly affected Vessel/Section: _____

⌊_⌋ Vessel injury Vessel: _____

⌊_⌋ Wound infections, wound healing disorder

⌊_⌋ Blood loss > 500 ml ⌊_⌊_⌊_⌊_⌋ ml

⌊_⌋ Ileus

⌊_⌋ Sepsis

⌊_⌋ **Symptomatic** Lymphocele: Intervention YES ⌊_⌋ NO ⌊_⌋

Procedure: _____

⌊_⌋ Nerve irritations (sensitive/motoric)

⌊_⌋ Other: _____

Please supply detailed information concerning the respective complications and forms of therapy (according to LENT-SOMA- classification):

_____

_____

_____

Signature of examining physician Date (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 8- Lymph Node Status

Pat.-ID-No	**Pseudonym**	
⌊_⌊_⌊_⌊_⌊_⌊_⌋	⌊_⌊_⌋	⌊_⌊_⌊_⌊_⌋
shall be issued by the study centre	surname Pat.(the last 2 letters)	Pat.-year of birth YYYY

Date ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ (dd/mm/yyyy)

Pelvine lymph nodes, number removed: ⌊_⌊_⌊_⌋

⌊_⌋ affected, number: ⌊_⌊_⌊_⌋

⌊_⌋ not affected, number: ⌊_⌊_⌊_⌋

⌊_⌋ not examined

Paraaortal lymph nodes, number removed: ⌊_⌊_⌊_⌋

⌊_⌋ affected, number: ⌊_⌊_⌊_⌋

⌊_⌋ not affected, number: ⌊_⌊_⌊_⌋

⌊_⌋ not examined

Signature of examining physician Date (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 9- Chemotherapy

Pat.-ID-No	**Pseudonym**	
⌊_⌊_⌊_⌊_⌊_⌊_⌋	⌊_⌊_⌋	⌊_⌊_⌊_⌊_⌋
shall be issued by the study centre	surname Pat.(the last 2 letters)	Pat.-year of birth YYYY

Chemotherapy ⌊_⌋ Yes ⌊_⌋ No

Administered Chemotherapy Agent: _____

Dosage /qm KOF or AUC: _____

Dosage absolute: _____

Date 1. Cycle: ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ (dd/mm/yyyy)

Date 2. Cycle: ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ (dd/mm/yyyy)

Date 3. Cycle: ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ (dd/mm/yyyy)

Date 4. Cycle: ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ (dd/mm/yyyy)

Date 5. Cycle: ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ (dd/mm/yyyy)

Dosage reduction: ⌊_⌋ No ⌊_⌋ Yes

If yes, reason: _____

Delay dosage: ⌊_⌋ No ⌊_⌋ Yes ⌊_⌋ dose was administered late

If yes, reason: _____

Completely executed: ⌊_⌋ Yes ⌊_⌋ No

If no, reason: _____

_____

Signature of examining physician Date (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 10 Acute Toxicity Chemotherapy

Pat.-ID-No

shall be issued by the study centre

Pseudonym

surname Pat.(the last 2 letters)

Pat.-year of birth YYYY

(according to http://ctep.cancer.gov/reporting/CTC-3test.html)

Toxicity Degree	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11
Leukocytes											
Thrombocytes											
Haemoglobin											
Creatinine i.S.											
Creatinine Cl.											
Urea											
Bilirubin											
Nausea											
Vomiting											
Neurotoxicity											
Ototoxicity											
Hospital Admission* Y/N											
Date											

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Marnitz S, *et al*. *Int J Gynecol Cancer* 2020; 30:1855–1861. doi: 10.1136/ijgc-2020-001973

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 11- Radiation Therapy

Pat.-ID-No	**Pseudonym**	
⌊_⌊_⌊_⌊_⌊_⌊_⌋	⌊_⌊_⌋	⌊_⌊_⌊_⌊_⌋
shall be issued by the study centre	surname Pat.(the last 2 letters)	Pat.-year of birth YYYY

Radiation Therapy ⌊_⌋ Yes ⌊_⌋ No

1. Percutaneous Radiation ⌊_⌋ Yes ⌊_⌋ No

Single dosage ⌊_⌊_⌊_⌋ Gy

Dosage beaker ⌊_⌊_⌊_⌋ Gy

Dosage Paraaortal Lymph Drainage Pathways ⌊_⌊_⌊_⌋ Gy

Dosage Parametrium right ⌊_⌊_⌊_⌋ Gy

Dosage Parametrium left ⌊_⌊_⌊_⌋ Gy

Middle Block ⌊_⌋ Yes ⌊_⌋ No with ⌊_⌊_⌊_⌋ Gy

2. Afterloading ⌊_⌋ Yes ⌊_⌋ No

Nominal single dosage tumour enveloping: ⌊_⌊_⌊_⌋ Gy

Number pf Applications ⌊_⌊_⌊_⌋

Nominal total dosage tumour enveloping: ⌊_⌊_⌊_⌋ Gy

<u>Total Treatment Time in Days</u>

(Percutaneous Therapy und Afterloading) ⌊_⌊_⌊_⌋

Therapy pauses ⌊_⌋ Yes ⌊_⌋ No

Beginning (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ End (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Total duration of Therapy Pauses in Days: ⌊_⌊_⌋

Signature of examining physician Date (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 12- Acute Toxicity Radiation Therapy

Pat.-ID-No ⌊_____⌋ shall be issued by the study centre

Pseudonym ⌊__⌋ surname Pat.(the last 2 letters) ⌊____⌋ Pat.-year of birth YYYY

(according to http://ctep.cancer.gov/reporting/CTC-3test.html) *due to therapy-induced toxicity

Toxicity RTOG Degree	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11
Skin											
Mucous Membrane											
Intestine											
Bladder											
Vagina											
Other Y/N* Specify											
Hospital Admission* Y/N											

Signature of examining physician Date ⌊_____⌋ (dd/mm/yyyy)

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 13- Remission Status

Pat.-ID-No	**Pseudonym**	
⌊_⌊_⌊_⌊_⌊_⌊_⌋	⌊_⌊_⌋	⌊_⌊_⌊_⌊_⌋
shall be issued by the study centre	surname Pat.(the last 2 letters)	Pat.-year of birth YYYY

Remission Status *6-8 Weeks after Therapy*

Date of the examination ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ (dd/mm/yyyy)

Imaging (MRT)	**Gynaecological Examination**
⌊_⌋ Complete Remission	⌊_⌋ Complete Remission
⌊_⌋ Partial Remission	⌊_⌋ Partial Remission
⌊_⌋ Stable Affection	⌊_⌋ Stable Affection
⌊_⌋ Progress	⌊_⌋ Progress
⌊_⌋ c.A.	⌊_⌋ c.A.

Determination of Complete Remission (dd/mm/yyyy): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Abrasio (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

⌊_⌋ No evidence of tumour cells

⌊_⌋ vidence of tumour cells

Signature of examining physician Date (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 14- After-care

Pat.-ID-No	**Pseudonym**	
⌊_⌊_⌊_⌊_⌊_⌊_⌋	⌊_⌊_⌋	⌊_⌊_⌊_⌊_⌋
shall be issued by the study centre	surname Pat.(the last 2 letters)	Pat.-year of birth YYYY

Date of the examination ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ (dd/mm/yyyy)

Weight (kg) ⌊_⌊_⌊_⌋

Karnofsky- Index ⌊_⌊_⌋

Imaging ⌊_⌋ Yes ⌊_⌋ No

⌊_⌋ CT

⌊_⌋ MRT

⌊_⌋ Other: _____

Suspicion of Tumour:

⌊_⌋ Yes ⌊_⌋ No

Tumour Localisation: _____

Tumour Findings: _____

Histologically verified recurrence: ⌊_⌋ Yes ⌊_⌋ No

_____

Signature of examining physician Date (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 15- Late Toxicity

Pat.-ID-No	**Pseudonym**	
⌊_⌊_⌊_⌊_⌊_⌊_⌋	⌊_⌊_⌋	⌊_⌊_⌊_⌊_⌋
shall be issued by the study centre	surname Pat.(the last 2 letters)	Pat.-year of birth YYYY

Date of the Examination (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Tumour Associated Morbidity:

⌊_⌋ Yes ⌊_⌋ No

If yes, please specify:

_____

_____

_____

Therapy-associated Morbidity:

⌊_⌋ Yes ⌊_⌋ No

If yes, please specify:

_____

_____

_____

_____

Signature of examining physician Date (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy

Form 16- Conclusion

Pat.-ID-No	**Pseudonym**	
⌊_⌊_⌊_⌊_⌊_⌊_⌋	⌊_⌊_⌋	⌊_⌊_⌊_⌊_⌋
shall be issued by the study centre	surname Pat.(the last 2 letters)	Pat.-year of birth YYYY

Date pf last Follow-Up / or date of death: ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ (dd/mm/yyyy)

Survival Status **dead** ⌊_⌋ ⌊_⌋ **alive**

Cause of Death

- ⌊_⌋ Cervix Carcinoma
- ⌊_⌋ secondary malignant tumour
- ⌊_⌋ toxicity of the study treatment
- ⌊_⌋ other non tumour-related reasons
- ⌊_⌋ unknown

Reason for withdrawal

- ⌊_⌋ death
- ⌊_⌋ lost to follow up
- ⌊_⌋ treatment abandoned
- ⌊_⌋ other reasons:

Signature of examining physician Date (dd/mm/yyyy) ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on the choice of therapy and the oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy.

20.2 Model Patient Information and Declaration of Consent

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

PATIENT INFORMATION

Dear Patient,

In the following, we should like to present to you our study,

"Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy".

1. Introduction

You have been diagnosed with cervical cancer. The stage classification (so-called FIGO-System) of the cervical cancer is based on the gynaecological examination and a few additional examination methods. The lymph-node metastases, which are decisive for the prognosis and for selecting the therapy are not taken into account in this process and are often not detectable, neither in the computer tomography (CT) nor in the magnetic resonance tomography (MRT). Hence, for very many patients, the tumour stage is underestimated, which leads to under-treatment.

2. Study Objective

The aim of the study is to demonstrate that the operative examination of the pelvic and abdominal cavity, the systematic examination of the lymph nodes and removal of affected lymph nodes prior to commencing radio-chemotherapy leads to a therapy adequately adjusted to the tumour stage. It shall be examined whether this leads to an enhancement of disease-free survival. The only new element contained in this study is the operative examination and removal of the lymph nodes; all other methods in the clinical routine are tried and proven and shall be applied according to the current state of the art and the respective legal directives.

3. Procedure and Duration of Participation

Each patient is allocated at random (Randomisation) to one of the two groups (Arm A and Arm B). Your attending doctors have no influenceon this. Patients in **Arm A** receive an operative lymph node examination (e.g. using the "keyhole method", i.e.

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laparoscopic or "open"). Since, in the course of this, the stage of the disease might change, we call this arm,"the arm with the corrected FIGO stage". Subsequently, on the basis of the findings obtained, standard radio-chemotherapy is planned and carried out under consideration of the findings of the staging, which are included in the therapy schedule.

In **Arm B,** primary radio-chemotherapy is performed without operative examination of the lymph node status. Only in the event of enlarged paraaortal lymph nodes, will their status be clarified by means of a CT puncture. This does not constitute standard procedure, but is essential for the determination of the radiation therapy fields. In the case of lymph nodes without pathological findings, no paraaortal radiation will be carried out, thus sparing you from unnecessary side-effects. Should the lymph nodes be affected, the paraaortal region will be included in the radiation field.

In the first three years, a clinical examination and a gynaecological ultrasonic and other examinations will be performed every three months. The questionnaire for recording life quality shall serve to examine the effects of the disease and of the treatment on quality of life. The after-care examinations will be carried out regularly over a period of at least four years, initially at intervals of every three months. These examinations shall assure the quality of the therapy and shall also serve to ensure your own safety.

4. Possible Risks

Every operation can involve side-effects. At the Charité, minimal invasive interventions are carried out on the lymph nodes using a so-called laparoscopic operation technique ("Keyhole Operation"). No abdominal incision is performed. At various locations between the diaphragm and the iliac crest, a total of five small incisions are made, through which the instruments (trocars)are inserted into the operation region.

The following complications may occur: occasional delayed wound healing (<1%), frequent occurrence of usually harmless lymphatic cysts (ca. 15%), which only require treatment if they grow larger or become inflamed and/or if they press upon the blood vessels, which can lead to the formation of blood clots (thromboses). The removal of the lymph glands may lead to chronic swelling in the legs (5%) which, however, rarely needs treatment (lymph drainage) Further complications caused by the operation can involve nerve damage, temporary problems with the bladder and bowel evacuation and sensitivity disorders in the genital and anal regions or in the thighs. Damage to the ureter and blood vessels, sometimes accompanied by heavy bleeding, is very rare (<1%). If it was decided to select a laparoscopic access, it shall be at the discretion of the operator whether to use the alternative of a conventional abdominal incision in order to prevent risks for your health.

5. Possible Benefits

As a study patient, you will be under continual monitoring. In this way, side-effects can be recognized quickly and treated accordingly. As a patient at the centre for cervical cancer, the competent doctors are there at your side. The object of the study is to determine whether the use of lymphadenectomy prior to beginning with the radio-chemotherapy leads to an improved prognosis. Currently available data shows that this concept does not lead to an increase in therapy-related side-effects.

6. Circumstances that would lead to abandoning the study

In the event of reservations in regard to safety, or if an intermediate evaluation should show that another therapy arm is significantly superior, the study will be discontinued by the study director. You yourself can withdraw your consent to participation in the study at any time. This will not result in any disadvantages for you.

7. Data Protection

By signing the declaration of consent, you declare that you are in agreement that the study physician and his colleagues may collect and process your personal-related data for the purposes of the aforementioned study. Person-related data are, for example, your date of birth, sex, data in relation to the disease , such as, size of tumour , tumour marker, lymph-node affection or other personal data collected during your participation in the study or in the course of follow-up examinations. The study physician will use your person-related data for the purposes of administration, execution of the study, research and statistical evaluation. You are entitled to receive information concerning all person-related data collected by the study physician, and have the right to have corrections made in the event of discrepancies. Should you have any queries, please ask the study physicians. You will find the address and telephone number at the end of the form.

The findings of this study may be published in the relevant scientific literature, whereby your identity will remain anonymous. At any time, you may refuse the further processing of your data collected during the study and are entitled to demand that it be erased and/or destroyed.

This study is a therapy optimisation study. New drugs of or unknown therapies will not be used. Every single component of the therapy has been tried and proven in other studies and routine applications. The study was initiated by the clinics for gynaecology and radiation therapy and, moreover, it is also performed at other German university clinics and hospitals. There are no sponsors for the study. For the statistics and data documentation, funds are applied for from the German Cancer Aid.

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on the choice of therapy and the oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy.

Should you have any questions or problems, please contact us under the following numbers:

Dr. Paulick, Clinic for Gynaecology and Obstetrics, Tel. +49 (030) 450664073 and/or +49 (030) 450664443; Dr. Bischoff, Clinic for Radiation Therapy, Tel. +49 (030) 450627346. Outside of office hours you can obtain the telephone number of the duty physician of the clinics via the telephone number of the Com-Centre +49 (030) 450 577044

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on the choice of therapy and the oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy.

Clinic for Radiation Therapy
Charité Campus Mitte and CVK,
Prof. Dr. med. V. Budach

Clinic for Gynaecology, Charité
Campus Mitte and CBF
Prof. Dr. A. Schneider M.P.H.

Declaration of Consent

I hereby declare that I,

Christian Name, Name _____ date of birth _____

Address _____

that I have been informed by Dr._____

verbally and in writing concerning the benefits and possible disadvantages arising for me from the therapy optimisation study "Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy",

which will be carried out by the Clinic for Gynaecology and Radio-oncology of the Charité, and that I have received sufficient opportunity to clarify my questions in this respect in consultation with the study physician. I have understood the study design and the patient information presented to me and have received a copy of this information and this declaration of consent. I am in agreement that a study physician may contact my attending physician in the framework of this study. I have the right to discontinue the treatment in the framework of the study at any time and, of course, no disadvantages whatsoever shall arise for me should I decide to refused randomisation.

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on the choice of therapy and the oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy.

Information regarding the study that may influence my willingness to participate will be forwarded to me in good time.

I am willing to participate in the scientific investigation in the framework the study. I am aware that I am entitled to withdraw my consent, at any time, without stating any reasons and without any disadvantageous consequences for me and that, at any time, I may refuse the further processing of my date.

Declaration of Consent to the Processing of my Data

I hereby declare my consent that the data/information collected in the framework of this study concerning my health may be encrypted, recorded on electronic data media and processed, and that the anonymised study findings may be published. I also declare my consent that the aforesaid data may be communicated to the Institute for Biometry and Clinical Epidemiology of the Charité University Medicine Berlin, Charitéplatz 1, 10117 Berlin for the purposes of the aforementioned study.

In addition, I am in agreement that my tissue may be removed, encrypted, examined and stored in the framework and for the purposes of this clinical study by the study physicians and/or the Laboratory for Tumour Immunology, Director PD Dr. rer. nat. A. Kaufmann, Charité University Medicine Berlin.

Berlin, dated signature of the study participant

_____ _____

I hereby declare that I have explained to the above named study participant the nature, significance, consequences and risks of the aforementioned study, verbally and in writing, and that I have given her a copy of this information as well as the declaration of consent.

Berlin, dated _____

Signature of the study physician responsible for informing the patients.

_____

Prospective, randomised and multi-centric therapy optimisation study for examining the influence of operative staging on the choice of therapy and the oncological findings for patients with cervix carcinoma of the FIGO stages IIB-IV after radio-chemotherapy.

20.3 FIGO und TNM Classification

TNM	FIGO	
TX		Primary tumour cannot be assessed.
T0		No indication of primary tumour-
Tis	0	Carcinoma in situ
T1	I	Carcinoma is strictly confined to the cervix uteri (propagation to the Corpus uteri remains unconsidered)
T1a	IA	Invasive carcinoma only identified microscopically All macroscopically recognizable lesions -even with surface invasion - classified under stage IB. The invasion is confined to a measured Stroma-Invasion with a maximum depth of 5 mm and a surface propagation of not more than 7 mm.
T1a1	IA1	Measured Stroma-Invasion of not more than 3 mm in depth and a surface propagation of not more than 7 mm.
T1a2	IA2	Measured Stroma-Invasion depth of more than 3 mm and not more than 5 mm with a surface propagation of not more than 7 mm.
T1b	IB	Clinically recognizable lesions, confined to the cervix uteri or subclinical lesions with larger dimensions than Stage IA.
	IB1	Clinically recognizable lesions, not larger than 4 cm.
	IB2	Clinically recognizable lesions, larger than 4 cm.
T2	II	Zervixkarzinom infiltriert jenseits des Uterus, aber nicht bis zur Beckenwand und nicht bis zum unteren Drittel der Vagina
T2a	IIA	Without infiltration of the parametrium. Infiltration of the upper 2/3 of the vagina.
T2b	IIB	With infiltration of the parametrium, but no propagation to the pelvic wall.
T3	III.	Cervix carcinoma spreading to the pelvic wall and affecting the lower third of the vagina, and causing hydronephrosis or mute kidney.
T3a	IIIA	Tumour affecting the lower third of the vagina, no propagation to the pelvic wall.

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T3b	**IIIB**	**Tumour propagating to the pelvic wall or causing hydronephrosis or mute kidney**
T4	**IV-**	**Tumour infiltrating the mucous membrane of the bladder of rectum and/or exceeding the bounds of the pelvis minor.**
T4	**IVA**	**Propagating to the neighbouring organs of the pelvis.**
T4	**IVB**	**Propagation to removed organs (remote metastases).**

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20.4 Activities Index (Karnofsky)

The Condition of the Patient:

Normal condition, no disorders, no manifestation of disease	**100%**
Normal performance, minimal disease symptoms	**90%**
Normal performance under exertion, minor disease symptoms	**80%**
Limited performance, and not able to work, can care for self	**70%**
Limited performance, occasionally needs help from other persons	**60%**
Limited performance, needs nursing and medical care, not permanently bedridden	**50%**
Patient is bedridden, need special care	**40%**
Patient is seriously ill, hospital care needed	**30%**
Patient is seriously ill, hospital care and supportive measures necessary	**20%**
Patient is moribund, disease and advancing rapidly	**10%**

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20.5 Information on Chemotherapeutic Agent Cisplatin

Cisplatin Dosage	- 40 mg/m2 KOF in 500 ml NaCl 0,9% more than 30 minutes before radiotherapy
Blood Test	- before every chemotherapy: liver and kidney count, Creatinine Clearance, electrolyte, Ca++ , Mg++ - Nadir: ca. Tag 10-14, BB test day 10
Cisplatin Administration	
Day 1 (to 3):	- 1000 ml NaCl - 8 mg Fortecortin + 5 mg Navoban in 250 ml NaCl 45 min prior to chemotherapy - Cisplatin in 500 ml NaCl for 30 min; parallel 250 ml Osmofundin - 1000 ml NaCl - Paspertin or Vomex with Bed., Fortecortin, 4-8 mg p.o. 4 & 8 hrs. after the infusion - 150 mg Ranitic for the night p.o. - Drip-rate must be >200 ml/hr.
Each 2.-4. Day after Chemo**:**	- 4 x 30 Tr. Paspertin, Fortecortin, 4-0-4 mg., Ranitic, 150 mg p.o. for the night. - Navoban, 5 mg daily, additionally, if necessary, for nausea Emend, 125 mg on chemotherapy day p.o., 2 and 3. Following day 80 mg p.o. -if necessary, from day 8 each after BB. With Neutropenia, stimulate if necessary.
ATTENTION !	**25% Dosage reduction in the rare case of leucocytopenia < 1,5/microlitres, thrombocytopenia < 80/microlitres, dosage reduction for GFR < 80 ml/ /min and depression of the medulla** **Mesna and Na-thiosulphate inactivate Cisplatin**

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Nephrotoxicity, Ototoxicity, Neurotoxicity, Hyperuricaemia, Myelosuppression. Rare Alopecia, Allergy, Fever, Electrolyte Displacement

Interaction with aminoglycosides, amphotericin B and high-ceiling diuretics

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20.6 List of Participating Centres

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20.7 Abbreviations

AGO	Working Group - Gynaecological Oncology
AIDS	Acquired Immunodeficiency Syndrome
AL	Afterloading
AUC	Area under the Curve
ARO	Working Group Radiological Oncology
CA 12-5	Cancer-Antigen 125
CDDP	Cisplatin
CEA	Carcino-embryonic Antigen
cm	centimetre
COPD	Chronic Obstructive Pulmonary Disease
CT	Computer Tomography
CTC	Common Toxicity Criteria
CYFRA 21-1	Cytokeratin Fragment
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ C-30	Questionnaire for the Verification of Life Quality
FDG-PET	[18F]-Fluoro-Desoxy-glucose Positron Emissions-Tomography
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
Gamma- GT	Gammaglutamyltransferase
GOG-Study	Gynaecological Oncology Group- Study
GOT	Glutamate Oxalacetate Transaminase
GPT	Glutamate Pyruvate Transaminase
HIV	Human Immunodeficiency Virus
HPV	Human Pathogenic Papilloma Viruses
IDNO	Identification Number
KOF	Body Surface
M.P.H	Master of Public Health
MRT	Magnetic Resonance Tomography
NYHA	New York Heart Association
PET	Positron Emission Tomography
QLQ	Quality of Life
RTOG	Radiation Therapy Oncology Group
SCC	Squamous Cell Carcinoma Antigen

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20.8 General Health and Well-being Questionnaire (LQ)

We are interested in gathering some information about you and your general state of health and well-being. Please complete the next section yourself by crossing the number that indicates the most accurate answer to the following questions about you. There are no "right" or "wrong" answers. Your information will be treated with strict confidentiality.

Please enter your initials here.....|_|_|_|_|

Your date of birth (day, month, year).....|_|_|_|_|_|_|

Today's date (day, month, year).....|_|_|_|_|_|_|

Identification Number (to be entered by study doctor).....|_|_|_|_|_|_|

		not at all	little	moderate	very
1.	Do you have difficulty in exerting yourself physically? (e,g, to carry a heavy shopping bag or suitcase)?	1	2	3	4
2.	Do you have difficulty in taking a long walk?	1	2	3	4
3.	Do you have difficulty leaving the house for a short stretch?	1	2	3	4
4.	Do you have to remain in bed or seated in an armchair during the day?	1	2	3	4
5.	Do you need help when eating, dressing, washing or using the toilet?	1	2	3	4

During the last few weeks:

		not at all	little	moderate	very
6.	Were you in any way limited in your work or during other daily occupations?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Did you have any pains?	1	2	3	4

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Please enter your initials here.....|_|_|_|_|

Your date of birth (day, month, year).....|_|_|_|_|_|_|

Today's date (day, month, year).....|_|_|_|_|_|_|

Identification Number (to be entered by study doctor).....|_|_|_|_|_|

---

	not at all	little	moderate	very
10. Were you forced to take a rest?	1	2	3	4
11. Did you have trouble sleeping?	1	2	3	4
12. Did you feel weak?	1	2	3	4
13. Did you have a lack of appetite?	1	2	3	4
14. Did you feel nauseous?	1	2	3	4
15. Did you vomit?	1	2	3	4
16. Did you have constipation?	1	2	3	4
17. Did you have diarrhoea?	1	2	3	4
18. Did you feel tired?	1	2	3	4
19. Did you feel hindered by pain in your everyday life?	1	2	3	4
20. Did you have difficulty in concentrating on something, e.g. reading the newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you feel worried?	1	2	3	4
23. Were you irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Did you have trouble remembering things?	1	2	3	4

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Please enter your initials here..... ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Your date of birth (day, month, year)..... ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Today's date (day, month, year)..... ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Identification Number (to be entered by study doctor)..... ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

---

	not at all	**little**	**moderate**	**very**
26. Has your physical condition or your medical treatment had a negative effect on your family life?	1	2	3	4
27. Has your physical condition or your medical treatment had a negative influence on your relationships or when doing things together with other people?	1	2	3	4
28. Has your physical condition or your medical treatment caused you financial difficulties?	1	2	3	4

Please cross one of the numbers from 1 to 7 that indicates the most accurate answer to the following questions about you:

29. How would you assess your general state of health during the last few weeks?

1	2	3	4	5	6	7
very bad						**excellent**

30. How would you assess your overall quality of life during the last few weeks?

1	2	3	4	5	6	7
very bad						**excellent**

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21. Literature

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