NPC-2016

A multicenter registry for nasopharyngeal cancer in children, adolescents and young adults

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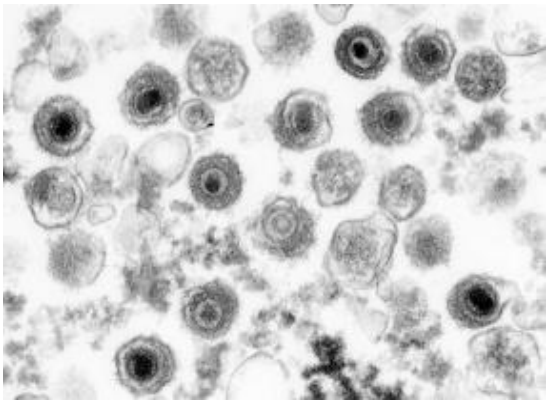

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1 General information

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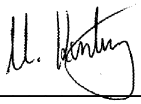

Aachen, 24.8.2017

1.3 Synopsis

Title:	NPC-2016 - A multicenter registry for nasopharyngeal cancer in children, adolescents and young adults
Short Title:	NPC-2016
Investigator:	Prof. Dr. med. Udo Kontny, Universitätsklinikum RWTH Aachen
Condition / Topic:	Nasopharyngeal Carcinoma
Objectives:	- Collect epidemiological information - Collect information on treatment and outcome to determine whether a relationship exists between outcomes and specific interventions - Collect information on late effects and quality of life - Assess the quality of treatment by the means of data collection, data check and an advisory service provided by the registry and the reference centers - Establishment of a tumor bank as a base for further biological studies to define new risk factors and to identify new targets for therapy
Secondary objectives:	3-, 5- and 10-year overall and event-free survival
Inclusion criteria:	- Confirmed diagnosis of nasopharyngeal carcinoma in patients ≤ 18 years - Informed consent by legal guardians and/or patient to contribute data to the registry In case of EBV-positive NPC WHO Typ IIb or III, patients older than 18 years of age can be included as well
Exclusion criteria:	Absence of informed consent by legal guardians and/or patient to contribute data to the registry.
Statistical methods:	The analysis of survival times and other quantitative and qualitative variables will be completed using suitable descriptive methods. Confidence intervals for all estimates will be computed.
Ethical considerations:	The registry will be conducted in accordance with the Declaration of Helsinki, the current revision of ICH, Guideline for GCP and the local law.

1.4 Synopse

Titel:	NPC-2016 – Multizentrisches Register zur Erfassung des Nasopharynxkarzinoms bei Kindern, Jugendlichen und jungen Erwachsenen
Kurztitel:	NPC-2016
Leiter:	Prof. Dr. med. U. Kontny, Universitätsklinikum RWTH Aachen
Thema:	Nasopharynxkarzinom
Ziele:	- Sammlung epidemiologischer Informationen - Sammlung von Informationen über die Behandlung und das Behandlungsergebnis sowie retrospektive Auswertung des Zusammenhangs zwischen Intervention und Ergebnis - Erfassung von Spätfolgen und Lebensqualität - Beurteilung der Qualität der Behandlung durch Datensammlung, Datenüberprüfung und Beratung durch das Studienzentrum und die Referenzeinrichtungen - Schaffung einer Tumorbank als Grundlage für zukünftige biologische Forschungsvorhaben zur Identifizierung neuer Risikofaktoren und Angriffspunkte für zielgerichtete Therapeutika
Sekundäre Ziele:	3-, 5- und 10-Jahres Gesamt- und Ereignis-freies Überleben
Einschlußkriterien:	- Diagnose eines Nasopharynxkarzinoms bei Patienten ≤ 18 Jahre - Einwilligung durch gesetzlichen Vertreter und/oder Patienten zur Datenweitergabe an das Register Im Falle eines EBV-positiven NPC WHO Typ IIb or III, können Patienten > 18 Jahre in das Register mit aufgenommen werden.
Ausschlußkriterien:	Fehlende Einwilligung durch gesetzlichen Vertreter und/oder Patienten zur Datenweitergabe an das Register
Statistische Methoden:	Einsatz geeigneter deskriptiver Methoden zur Analyse des Überlebens und anderer quantitativer wie qualitativer Variablen; Erstellung von Konfidenzintervallen für alle ermittelten Größen
Ethikrichtlinien:	Das vorliegende Register wird gemäß der geltenden gesetzlichen Bestimmungen und Richtlinien sowie der aktuellen ICH-Richtlinie für GCP durchgeführt. Die Richtlinien der Deklaration von Helsinki werden eingehalten.

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1.7 List of abbreviations

AJCC	American Joint Committee on Cancer
AMG	Arzneimittelgesetz
BSA	Body surface area
CBC	Complete blood count
CDDP	Cisplatin
CR	Complete response
CRP	C-reactive protein
CT	Computer tomography
d	Day
DNA	Desoxyribonucleic acid
DPD	Dihydropyrimidine dehydrogenase
DSS	Disease-specific survival
EA	Early antigen
EBER	Epstein-Barr virus-encoded small RNA
EBNA	Epstein-Barr virus nuclear antigen
EBV	Epstein-Barr virus
ED	Single dose
EEG	Electroencephalography
EFS	Event-free survival
FU	5-Fluorouracil
GOT	Glutamic oxaloacetic transaminase
GPOH	Gesellschaft für Pädiatrische Onkologie und Hämatologie
GPT	Glutamic pyruvic transaminase
Gy	Gray
HLA	Human leucocyte antigen
IFN-ß	Interferon-ß
IFN-γ	Interferon-γ
KI	Karnowsky-index
KM	Contrast medium
LCV	Leucovorin
LMP1	Latent membrane protein
MRT	Magnetic resonance tomography
MTX	Methotrexate
NKC	Non-keratinizing carcinoma
NSE	Neuron-specific enolase
NUC	Nuclear medicine
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
POG	Pediatric Oncology Group
PR	Partial response
rhuG-CSF	Recombinant human granulocyte colony stimulating factor
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SCC	Squamous cell carcinoma
SD	Stable disease
SE	Spin-echo sequence
STIR	Short-T1 inversion recovery
TRM	Treatment-related mortality
UICC	Union internationale contre le cancer
VCA	Viral capsid antigen
WHO	World Health Organisation

ZEBRA	BamHI Z EBV replication activator

2 Background: Current knowledge of nasopharyngeal cancer

2.1 Epidemiology

Nasopharyngeal carcinoma (NPC) is a rare neoplasm arising from epithelial cells of the nasopharynx. Its incidence varies between geographical locations, with the highest incidence occurring in adults in Southeast Asia. The age distribution of NPC is bimodal, with one peak arising in young adolescents and another one in patients between 55 and 59 years of age [1]. In Germany, NPC makes up about 0.2% of all neoplasms under the age of 18, with an incidence rate of 0.1 per 100,000 persons between 15 and 17 years of age [2]. Epidemiological studies from the United Kingdom report an incidence of about 0.3 to 0.4 per 100,000 persons across all age groups resulting in about 200 newly diagnosed patients per year [3]. In Southeast Asia environmental factors such as the consumption of certain herbs, salted fish and smoking have been described to be associated with an increased risk for NPC [4]. In addition, genetic factors, indicated by the occurrence of familial cases, association of NPC with certain HLA-subtypes and polymorphisms in host innate immune sensor genes influence the predisposition for this tumor [5,6].

2.2 Pathogenesis

NPC presents as a complex disease caused by an interaction of the oncogenic gamma-herpes virus Epstein-Barr virus (EBV), environmental, and genetic factors, in a multistep carcinogenic process [7]. A monoclonal EBV infection is found in more than 98% of pre-invasive lesions [8]. The EBV-infected epithelial cells express a restricted group of latent genes (type II latency) such as EBV nuclear antigen 1 (*EBNA1)*, latent membrane protein 1 (*LMP1), LMP2A* and Epstein-Barr virus-encoded small RNAs (*EBERs)* [9]. *In vitro* and *in vivo* models have shown that especially LMPs play a major role in malignant transformation of infected nasopharyngeal epithelial cells. More recently, evidence that the EBV BART microRNAs contribute to the malignant transformation has accumulated [10]. An aberrant immune response to EBV with high titers of IgA against viral capsid antigen (VCA) and early antigen (EA) is seen early in disease and has been used together with circulating plasma EBV-DNA for screening in high-risk areas [11-13]. EBV strains found in NPC induce an unusually strong virus replication in infected cells that might contribute to aberrant immune responses [14]. Furthermore, these strains infect epithelial cells much more efficiently than strains found elsewhere, suggesting that NPC is caused by particular EBV strains [14]. Next-generation sequencing of NPC tumors revealed a distinct mutational signature with alterations in pathways responsible for chromatin modification, autophagy and ERBB-PI3K signaling [15].

2.3 Clinical Presentation

Young patients with NPC frequently present with symptoms resulting from mass effect. Nasal symptoms, such as epistaxis and nasal obstruction are almost always present, and are secondary to the presence of the tumor in the nasopharynx. Secondly, auditory symptoms such as hearing loss and tinnitus occur, which are related to dysfunction of the Eustachian tube caused by latero-posterior extension of the tumor into the paranasopharyngeal space. Thirdly, cranial nerve palsies are present, commonly affecting the fifth and sixth cranial nerves and resulting from upward extension of the tumor leading to skull base erosion; patients also might experience headache, diplopia, facial pain and numbness. A retrospective analysis of 4,768 patients identified the following symptoms at presentation: neck mass (75.8%), nasal (73.4%), aural (62.4%), headache (34.8%), diplopia (10.7%), facial numbness (7.6%), weight loss (6.9%), and trismus (3.0%). The physical signs present at diagnosis were enlarged neck node (74.5%) and cranial nerve palsy (20.0%) [16]. Since

nasal and auditory symptoms are non-specific and a thorough examination of the nasopharynx is not easy to perform, the majority of NPC patients are only diagnosed when the tumor has reached a locally advanced stage. Indeed, up to 90% of patients present with lymph node metastases. In about 5-11% of patients distant metastases are detected at diagnosis involving bones (67%), lungs (20%), liver (30%), bone marrow (23%), and mediastinum [17,18].

2.4 Diagnosis

Histological analysis of a biopsy specimen is mandatory for the diagnosis of NPC. Prior to biopsy, mirror examination of the nasopharyngeal space for direct visualization of the tumor and MRI of the nasopharynx, skull base and neck including all cervical and supraclavicular lymph node regions are recommended (**Table 1**). MRI is preferred over CT, since it more precisely describes deep primary tumor infiltration [19].

Table 1: Cervical lymph node grouping according to the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery [20]

Sublevel IA	Submental
Sublevel IB	Submandibular
Sublevels IIA and IIB	Upper jugular
Level III	Middle jugular
Level IV	Lower jugular
Sublevels VA and VB	Posterior triangle group
Level VI	Anterior compartment group

Nasopharyngeal carcinomas are categorized along the WHO classification modified by Krüger and Wustrow [21] (**Table 2**). The classification indicates the degrees of lymphoid infiltration, whereby undifferentiated NPC with lymphoid infiltration corresponds to the lymphoepithelioma described by Schmincke in 1921 and non-keratinizing carcinoma with lymphoid stroma to the tumor characterized by Regaud in the same year [22,23]. In children and adolescents most tumors are of type III histology, the remaining ones type II [18]. Both type II and III tumors are EBV-associated, whereas type I is not [24].

Table 2: WHO classification of nasopharyngeal carcinoma modified by Krüger and Wustrow [21]

Typ I	Squamous cell carcinoma
Typ IIa	Non-keratinizing carcinoma without lymphoid stroma
Typ IIb	Non-keratinizing carcinoma with lymphoid stroma
Typ IIIa	Undifferentiated carcinoma without lymphoid stroma
Typ IIIb	Undifferentiated carcinoma with lymphoid stroma

2.5 Staging

Staging should include PET(/CT), chest-CT and MRI-abdomen for detection of distant metastases. In case of lesions suspicious of bone involvement on PET or MRI, a technetium bone scan is recommended. Also, EBV-serology, including anti-VCA-IgA and EBV-PCR are recommended. Tumor stages are defined by the classification of the International Union against Cancer (UICC) and the American Joint Committee of Cancer (AJCC) [25] (**Table 3 and 4**). MRI, PET(/CT), anti-EBV-VCA-IgA and EBV-PCR are useful parameters for monitoring response to therapy and are recommended to be repeated after neoadjuvant chemotherapy, after radiotherapy and after maintenance therapy with interferon-ß. In the NPC-2003 study all tumors were PET-positive at initial diagnosis or at relapse [26]. Changes in 18F-FDG uptake during therapy have been shown to be of prognostic value [27]. As

shown in the NPC-2003 study the dose of radiotherapy to the tumor could be safely reduced from 59.4 Gy to 54.4 Gy in patients who are in complete remission by MRI and PET after neoadjuvant chemotherapy.

Table 3: TNM-classification of nasopharyngeal carcinoma according to the International Union against Cancer (UICC) and American Joint Committee of Cancer (AJCC) system 8th edition [25]

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal fossa
T2	Tumor with parapharyngeal extension, prevertebral, medial and lateral pterygoid muscles
T3	Tumor involves bony structure (skull base, cervical vertebra) and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, or orbit, or involvement beyond the lateral surface of lateral pterygoid muscle, parotid gland

Regional lymph nodes (N)

NX	Regional nodes cannot be assessed
NO	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) ≤ 6cm in greatest dimension, above caudal border of cricoid cartilage and/or unilateral or bilateral retropharyngeal lymph nodes ≤ 6cm in greatest dimension (midline nodes are considered ipsilateral nodes)
N2	Bilateral metastasis in cervical lymph node(s) ≤ 6cm in greatest dimension, above caudal border of cricoid cartilage (midline nodes are considered ipsilateral nodes)
N3	Metastasis in a lymph node(s) > 6cm and/or below caudal border of cricoid cartilage (regardless of laterality)

Distant metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Table 4: Stages of nasopharyngeal carcinoma according to the International Union against Cancer (UICC) and American Joint Committee of Cancer (AJCC) system [25]

Stage	**T**	**N**	**M**
0	Tis	N0	M0
I	T1	N0	M0

II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
	T Any	N3	M0
IVB	T Any	N Any	M1

2.6 Treatment

As NPC is a radiosensitive neoplasm and tumors are usually not amenable to complete surgical excision due to their location, radiotherapy has been traditionally the treatment of choice. Several randomized trials over the last 20 years have shown a benefit for concomitant radiochemotherapy in loco regionally advanced disease in adults with regards to overall survival, event-free survival and relapse rate [28]. Radiation dosages of around 70 Gy to the primary tumor and 50 Gy to the lymph nodes are considered as standard in adults; combinations of cisplatin and 5-fluorouracil are mostly used for chemotherapy. With this concept 5-year progression free survival rates of about 70% have been achieved [29]. Currently, the role of sequential therapy consisting of induction chemotherapy, adjuvant chemotherapy or both is being investigated in several phase III clinical trials in adults.
In children and adolescents with NPC, sensitivity to chemotherapy has been shown as early as in the mid-70s [30]. There have been several retrospective studies on children and adolescents with NPC, most of them with less than 50 patients, mostly heterogeneous for the type of chemotherapy used and the dosage of radiotherapy applied, reporting a 5-year overall and disease-free survival of 41%-91% and 47%-85%, respectively [31-38]. NPC in children and adolescents has so far been prospectively studied only in 5 clinical trials [26,30,39-41]. Due to the low incidence of the disease in children and adolescents, none of these studies included a randomized question to be answered.

2.6.1 Treatment within the NPC-GPOH studies

The NPC-91-GPOH study was the first multicenter study for the treatment of NPC in children, adolescents and young adults [40]. 68 patients were registered, among them 5 patients with metastatic disease. Of the 59 protocol-patients (58 “high risk” patients (stage III and IV) and one “low risk “patient, median age 13 years, range 8-25) the high risk patients were treated with induction chemotherapy consisting of 3 cycles of methotrexate, cisplatin and 5-fluorouracil, radiotherapy with a dosage of 59 Gy to the primary tumor and 45 Gy to loco regional lymph nodes and maintenance therapy with interferon-ß for 6 months. The estimated overall survival for the protocol patients after 9 years was 95% and the disease-free survival 91%.
Therapy was complicated by severe mucositis requiring total parenteral nutrition in 46% of patients and dose reductions in subsequent cycles of chemotherapy in 30% of patients. Therefore, methotrexate was omitted in the NPC-2003 study [26]. In addition, due to results on the benefit of concomitant radiochemotherapy in adults [42], cisplatin was given for two weeks during radiotherapy. A third change to the NPC-91 study in 2003 was the reduction of the radiation dose to 54 Gy in patients with complete tumor remission after induction chemotherapy. The study resulted in an overall survival of 97% after a median-follow up of

30 months and an event-free survival of 92%. Follow up after 52 months showed an overall survival of 93% and an event-free survival of 92% (unpublished) (**Fig. 1**).

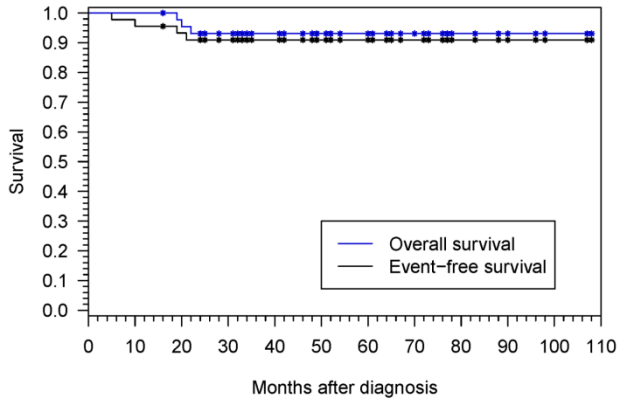

Fig. 1. Kaplan-Meier curve illustrating overall and event-free survival for patients of the GPOH-NPC-2003 study after a median follow up of 52 months. Asterixes indicate censored observations. [non published]

The NPC-91 and NPC-2003 studies are unique for the following four reasons: (1) both together encompass the largest number of children and adolescents with NPC treated in a prospective study. (2) The NPC-93 and NPC-2001 trials are the only trials for NPC which used interferon-ß as maintenance therapy. The latter fact was mainly due to the unavailability of this drug in other countries than Germany. (3) Overall and event-free survival in the two studies were higher compared to the ones reported by other prospective trials on NPC. Since in the Italian study, 5 of the 46 patients had metastases at diagnosis, outcome for their patients with loco regional disease appears to be similar. (4) Compared to the other prospective trials, the dosage of radiation to the primary tumor was lowest in the NPC-2003 trial.

3 Objectives

3.1 Primary objectives

- Collect epidemiological information
- Collect information on treatment and outcome to determine whether a relationship exists between outcomes and specific interventions
- Collect information on late effects and quality of life
- Assess the quality of treatment by the means of data collection, data check and an advisory service provided by the registry and the reference centers
- Establishment of a tumor bank as a base for further biological studies to define new molecular risk factors and to identify new targets for therapy

3.2 Secondary objectives:

3-, 5- and 10-year overall and event-free survival

4 Inclusion into the registry

4.1 Inclusion criteria:

1. Confirmed histological diagnosis of nasopharyngeal carcinoma in patients ≤ 18 years by reference pathology

2. In case of EBV-positive NPC WHO Typ IIb or III, patients older than 18 years of age can be included as well

3. Informed consent by legal guardians and/or patient to contribute data to the registry

4.2 Exclusion criteria:

Absence of informed consent by legal guardians and/or patient to contribute data to the registry

5 Procedures

Information on the registry and all documents are provided by the NPC registry coordinating team via the NPC homepage

5.1 Patient Registration

Informed consent

If a patient is considered eligible for the NPC registry, the investigator will inform the patient and/or his/her legal representative about the study and ask the patient and/or his/her legal representative for written consent **(Forms A1)**. It is imperative that written consent is obtained prior to any data transfer (including data on the patient registration fax). The original consent form will be filed with the patient's source documents, with a copy to be retained by the patient. If a patient enrolled will become 18 years old while the registry is still open, informed consent will be obtained from him being an adult.

Registration fax

To initiate patient inclusion, the investigator will send a registration fax **(Form A3.1)** to the NPC registry, including the surgical and local pathology report. Confirmation of local pathology by reference pathology has to be initiated at this point. According to a national agreement, every German patient <18 years of age has to be reported to the German Children's Cancer Registry (Deutsches Kinderkrebsregister) by a special registration form for all paediatric oncological studies (called "Krebs im Kindes- und Jugendalter - Erstmeldung") **(Form A3.2)**.

Enrollment into registry

Data are checked by the data manager and responsible physician of the registry centre for completeness. If inclusion criteria are met and exclusion criteria are ruled out, the patient is enrolled into the registry.

Confirmation of enrollment

Confirmation of the patient's enrollment into the registry is communicated to the responsible physician per fax. A NPC registry-specific patient identification number is also provided.

5.2 Data Registration

Initial Data

Initial data for patients from Germany < 18 years are transferred from the report of the German Children's Cancer Registry („Erstmeldung") into the NPC registry data base. Detailed data on all patients, including patients ≥ 18 years of age and patients from outside of Germany are obtained using an initial data form sheet ("Basisbogen") **(Form A3.3)** which is sent together with the confirmation of enrollment fax and a questionnaire on genetic predisposition **(Form A3.4)** to the local investigator.

Follow-up data (Forms A3.5 – A3.10)

To collect data on treatment performed and outcome CRFs are obtained at following time points:
CRF Chemotherapy: to be filled out for each cycle of chemotherapy
CRF Radiotherapy: to be filled out after radiotherapy
CRF Radiochemotherapy: to be filled out after radiotherapy

CRF Maintenance therapy: to be filled out after maintenance therapy, if performed
CRF End of therapy: to be filled out after the end of therapy
CRF Follow up: once a year, starting 1 year after tumor diagnosis

5.3 Reference Diagnostics

For assuring a high level of diagnostic accuracy in this rare tumor, local physicians are strongly encouraged to obtain reference diagnostics for the examinations cited below. Request forms for reference diagnostics are provided by the registry **(Forms A2)**. Results of reference diagnostics are sent directly to the local physician as well as the NPC registry. Data on the results of the reference diagnostics are entered by the data manager into the registry data base.

1. Pathology:
   Type of study: Confirmation of histology; subclassification of tumor
   Time points: Initially

2. Radiology:
   Type of study: Evaluation of MRI of tumor region + regional lymph nodes
   Time points: Initially, before and after radiotherapy, end of treatment, any time point: suspicion of relapse

3 Nuclear Medicine:
   Type of study: Evaluation of PET/CT
   Time points: Initially, before and after radiotherapy

4. EBV-Diagnostics:
   Type of study: EBV-PCR, EBV-Serology
   Time points: Initially, before and after radiotherapy, end of treatment, follow-up (q3m x 1y, q6m x 4y, q1y x 5y)

5. EBV-CTL-Diagnostics:
   Type of study: Analysis of precursor frequency of EBV-specific CTL
   Time Points: Initially; only in patients with metastatic disease or relapse

6. DPD-Genetics:
   Type of study: Analysis of DPD-exon 14 skipping mutation
   Time points: Before start of chemotherapy

7. Radiotherapy:
   Type of study: Assistance in planning of radiotherapy
8. Head and Neck Surgery
   Type of study: Assistance in planning of surgery
   Time points: relapse, amenable to surgery

5.4 Scientific projects and Biobanking

Tumor tissue, patient's blood sample as well as an oro-pharyngeal rinse are collected at the time of diagnosis and used for the projects listed below:

Investigations on the role of Epstein-Barr virus in the pathogenesis of nasopharyngeal carcinoma
Prof. Dr. med. Henri-Jacques Delecluse
Pathogenese infektionsbedingter Tumoren
Deutsches Krebsforschungszentrum
Abt. Tumorvirologie
Im Neuenheimer Feld 242
D- 69120 Heidelberg

Investigations on the immunity against Epstein-Barr virus in patients with nasopharyngeal carcinoma
Prof. Dr. med. Uta Behrends
Kinderklinik München Schwabing,
Klinikum rechts der Isar der
Technischen Universität München und
Klinikum Schwabing der StKM GmbH,
Kölner Platz 1
D-80804 München

Biomaterial will also be stored at the Centralized Biomaterial Biobank of the Medical Faculty of RWTH University (RWTH cBMB) to be used for future scientific projects, focusing on the detection of molecular risk factors and the identification of new therapeutic targets.

6 Data handling

Data are entered by the participating institutions into the paper forms provided by the NPC registry. Forms are then mailed to the NPC study centre. There, the data provided by the responsible physician will be processed, checked for consistency, and entered into an electronic data base. Implausible or missing data will be corrected or supplemented after contacting the responsible physician. Personal data of the patient will be handled with great care and according to the rules for data safety management and the legal requirements. Anonymisation of the data by request is possible at any time. Each patient receives a registry number for internal identification (recruitment log). The first 2 digits correspond to the country of the centre, the next 2 digits to the number of the site and the last 2 digits stand for the consecutively registered patients at the particular site, for example: 01-03-05 (country 1, centre 3, patient 5), so that each patient is numbered uniquely across the entire database.

All requirements of data protection legislation will be met. It is assured that all materials and data for scientific investigations will be pseudonymised in accordance with data protection legislation before scientific processing and at the time when clear data are not required for any reason. The legal guardians and/or patients will be informed that non-pseudonymised medical information will be forwarded for central review and counseling, but that only pseudonymised data will be passed on to further recipients.

7 Statistical analysis

Overall survival (OS) is defined as the time from diagnosis of NPC until last follow-up or event (death from any cause). Event-free survival (EFS) is defined as the time from diagnosis of NPC to last follow-up or first event (disease progression, relapse, secondary malignancy, death of any cause). Survival times will be calculated according to the Kaplan-Meier method and comparisons between different patient groups will be performed using the log-rank test.

The incidences of treatment-related mortality (TRM), relapse/disease progression, secondary malignancies and other late effects such as hearing loss, endocrine abnormalities will be calculated according to Kalbfleisch and Prentice. Subgroups will be compared with Gray's test. For multivariate analyses, the Cox proportional hazard regression model will be used. The analysis of the distribution of qualitative and quantitative variables will be done using suitable descriptive univariate and multivariate methods. Two-sided 95% confidence intervals will be calculated for all estimates.

Statistical analyses will employ the statistical software SPSS (Statistical Package for Social Sciences) and SAS (Statistical Analysis System). All analyses will be documented and saved. The transfer of the data from the study database will be performed after checking the data for plausibility.

8 Ethical and legal considerations

The high standard of diagnosis and treatment for nasopharyngeal carcinoma in children and adolescents in Germany has evolved within the unique national structure of pediatric oncology with nationwide registries and clinical trials offering central review and central counseling as important elements of quality control. Especially, in a rare tumor like nasopharyngeal carcinoma, patients will benefit from precise diagnostic evaluation and central review and central counseling as outlined. Therefore, it seems an ethical requirement to make these resources available to all future patients regardless of participation in a clinical trial.

The registry is based on the current version of the declaration of Helsinki (2013, Fortaleza, Brazil, see also https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). No treatment guideline is involved into it and there is no registry-related risk for participating patients. Data will be handled according to the national legal requirements. An ethics approval was obtained by the competent Ethics Committee for the registry and the associated consent forms. Approval by the local Ethics Committees is not required by law.

Before accepting patient data into the registry each patient will be counseled about the different parts of the registry and informed consent for data entry. A pro forma consent form for the local institution is provided and may be used. Patients will be informed on the right to withdraw from the registry at any time without giving reasons. Administrative documents, consent forms and copies of the registry documentation of a registry patient have to be kept according to set archival terms.

This prospective registry is not liable to §40 of the German “Arzneimittelgesetz” (AMG). The registry is therefore exempt from clinical trials insurance coverage according to law. Patients are covered by the public liability insurance of their hospitals.

9 Financial issues

The registry is supported by the parents’ organization „Förderkreis Hilfe für Krebskranke Kinder e.V. Aachen“.

10 Publication rules

Publication will be performed once critical numbers of patients have been enrolled into the registry. Preparation of publications will be led by the chairperson and can be delegated to members of the study section. For authorship the recommendations of the German Research foundation (DFG) will apply.

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