PLEASE NOTE: *This study has been imported from ClinicalTrials.gov without additional data checks.*

Trial Description

Title

Effectiveness of Adjuvant Radiotherapy in Patients With Oropharyngeal and Floor of Mouth Squamous Cell Carcinoma and Concomitant Histological Verification of Singular Ipsilateral Cervical Lymph Node Metastasis (pN1-state)

Trial Acronym

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URL of the trial

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Brief Summary in Lay Language

Radiotherapy with or without adjuvant chemotherapy represents an important column of modern therapy in advanced squamous cell originated tumours of the head and neck. However to date no studies are available which study the effectiveness of radiotherapy in patients with resected small tumours (T1, T2) and concomitant ipsilateral metastasis of a single lymph node (pN1) for general treatment recommendation. The present study is designed as non-blinded, prospective, multicenter randomized controlled trial (RCT) for comparison of overall-survival as primary clinical target in patients receiving radiation therapy vs. patients without adjuvant radiation following curative intended surgery. Aim of the study is to enroll 560 adult males and females for 1:1 randomization to one of the two treatment arms (radiation/non-radiation. Secondary clinical endpoints are as follows: Incidence and time to tumor relapse (locoregional relapse, lymph node involvement and metastatic spread), Quality of life as reported by EORTC (QLQ-C30 with H&N 35 module) and time from operation to orofacial rehabilitation.

Brief Summary in Scientific Language

Background

Prevailing curative intended therapeutic strategies combine radical resection of the tumor mass with a safety margin followed by radiation of the original tumor site and adjacent locoregional lymphatic drainage areas. To date selection of the individual therapeutic pattern is essentially guided by pre- and post-therapeutic TNM staging parameters.
Exceptionally for advanced tumors postoperative radiotherapy and optional combination with (radiosensitizing) chemotherapeutic agents is favorable and recommended. Interdisciplinary guidelines stated the following detailed recommendations for application of adjuvant radiation therapy:

- **non in sano resection if reoperation is impossible (R1-, R2-status)**
- **primary tumor status > pT2 and pN2, pN3**
- **extranodular spread of the disease**
- **lymphangiosis carcinomatosa**
- **facultative: pN1 According to these recommendations postoperative radiotherapy of advanced tumors is feasible while for small tumors indication for adjuvant therapy depends on further parameters like the pN findings. Here verification of more than one singular lymph node metastasis (pN2) leads to additional radiotherapy. In tumors with a diameter less than 4 cm (T1, T2) and concomitant verification of a single lymph node metastasis no explicit therapeutic recommendation is offered to date displaying radiation an optional complement for these cases. Meta-Analysis revealed only a few studies taking this special group of patients into account stating adjuvant radiotherapy an additional risk factor for overall survival, however small patient numbers, inhomogeneous group distribution and ambiguous risk factors exhibited a significant bias.**

The methodological key problems which had to be addressed in the protocol were the following:

- **extremely different treatment arms with strong preferences for one or the other therapy arm**
- **low number of eligible patients per center**

- Inclusion criterion (pN1) including a pathological diagnosis and surgical treatment with possible differences

- Radiation treatment as one arm with special need for quality control Thus the idea of presenting this paper is, to discuss how these specific issues were taken care of.

Methods/Design Study Design The study is designed as a non-blinded, prospective, randomized controlled clinical trial.

Study objectives Objective of the clinical study will be the investigation of two different patient collectives (irradiated/unirradiated) with pT1/2 primary and verification of a singular ipsilateral lymph node metastasis in parallel design in order to evaluate a possible significant benefit of radiation therapy. Investigation of further biological parameters will be concomitantly performed to assess a possible prediction of tumor progression and to evaluate surrogate markers of radioresistance. The following null hypothesis forms the basis of the present study: Radiation therapy will have no influence on the overall survival in patients with pT1/2, pN1 primary tumor. Secondary outcome variables include incidence and time to tumor relapse (locoregional relapse, lymph node involvement and metastatic spread), Quality of life as reported by EORTC (QLQ-C30 with H&N 35 module) and time from operation to orofacial rehabilitation.

Patients

Males and females with histological verified diagnosis of a primary squamous cell carcinoma of the oral cavity or the oropharynx are eligible. Inclusion criteria are as follows:

- maximum tumor diameter less than 4 cm in the pathohistological specimen irrespective of histological grading (pT1 or pT2)

- concomitant histological verification of a singular ipsilateral lymph node metastasis less than 3cm in diameter (pN1) without penetration of the lymph node´s capsule and without presence of lymphangiosis carcinomatosa

- radical resection of the tumor within adequate resection margins (R0)

- written informed consent from the patient

- adequate performance status ECOG Index ≤ 2 Patients with an age less than 18 and pregnant women are to be excluded. Further criteria of exclusion are reported drug addiction or intake of remedies with potential influence on compliance or impaired judgment. In addition patients with mental disorders or conceivable physical, familial or job related embarrassments which may preclude the patient to realize the study schedule. Moreover patients with physical impairment by inadequate treatment of derailed diseases e.g. untreated diabetes mellitus or acute heart insufficiency (ECOG-Index >2).

Study interventions Radiotherapy should begin within 6 weeks after the last surgical intervention, whereas a minimal postoperative healing period of at least 8 days should be respected. Causes for delay of intervention are to be documented. Application of radiotherapy defines group 1 versus the non irradiated group (group 2).

Surgical treatment The primary is considered radically resected if macroscopic and histologic evaluation approved resection margins without tumor residuals (R0 status). For surgical proceeding a safety margin of at least 1cm is established. For surgical considerations of lymph node resection the tumor localization is divided in level I (below occlusional plane) and level II (above occlusional plane) respecting pre-, postcanine or retromolar finding in addition. Classification of cervical regions follows the recommendations of Robbins from 2002. Hence, the neck is divided into 6 different sections.

Ipsilateral N0 state of cervical lymph nodes Pre- and postcanine localized tumors of level I require a selective neck dissection of the cervical level 1-3. In level I tumours of the retromolar triangle selective neck dissection of ipsilateral level 1-5 is proceeded. In level II tumors no selective neck dissection is considered.

Contralateral N0 state No neck dissection is performed Ipsilateral N1- N2 state For retromolar localized level I tumors a modified radical neck dissection is performed. If the tumor is localized pre- or postcanine intraoperative frozen sections of level 1 lymph nodes are evaluated. Positive intraoperative results lead to modified radical resection of level

1-5 lymph nodes. In case of negative results resection of the lymph nodes within level 1-3 is affiliated. Negative instantaneous sections in level II tumors require no lymph node dissection. All metastatic affection of level II-III lymph nodes necessitates modified radical neck dissection.

Contralateral N1-N2 state Instantaneous section is performed for level 1 lymph nodes. Modified radical neck dissection is performed in positive, resection of level 1-3 lymph nodes is conducted in negative results. Metastases spread in level 2-3 lymph nodes acquire modified radical neck dissection.

Lymph node therapy of midline tumors Midline tumors may require bilateral resection of lymph node echelons at risk. Bilateral modified neck dissection is performed for staging purposes if indicated. Contralateral lymph node dissection of the level 1-3 in precanine localized tumors is mandatory.

Technical conditions and practical execution of radiation therapy Radiotherapy is performed by photons of 4 to10 MeV or/and electrons of 6 to 15 MeV maximum energy. Individual 3 dimensional dose distribution calculation is mandatory and has to be made on the basis of a postoperative native computer tomogram. All patients are to be treated while immobilized by a custom made face mask made of thermoplast or equivalent. Clinical target volume definition compasses the original tumor site with a safety margin of 2 cm in each direction.

Floor of mouth, anterior tongue Irradiation of the anterior two third of the tongue as well as the anterior floor of mouth is irradiated by lateral opposing beams, while the maxilla is separated by insertion of a bite block.

Oropharynx, buccal plane, soft palate confined to one side For tumors of the buccal plane, the tonsilla, the soft palate and the retromolar triangle two types of planning target volume may be applied.

In case of negative contralateral cervical nodes an ipsilateral target volume for the primary is defined including the lymph nodes of group IB, IIA and IIB. Irradiation technique recommended is a two wedge fields typically angulated by 90 to 120 degrees. The ipsilateral

node levels III-V are treated by an anterior portal down to clavicle. The contralateral neck is spared.

Tumors of the lateral and dorsal pharyngeal wall and their lymphatic drainage (levels II, III, IV and V) are irradiated bilaterally with opposing beams. Irrespective of technique used 3 D conformal dose shaping is highly recommended.

Dosage and fractionation Target volume definition and dosage has to be performed according to the rules of ICRU report 50. At the primary tumor site and at involved lymph node levels a total dose of 59.4 Gy in 33 fractions within 45 days is scheduled. At electively irradiated volumes a total dose of 50.4 Gy in 28 fractions is scheduled. All fractions of 1.8 Gy each are given five times per week. In case of machine break down an additional fraction per week is recommended with an at least 6 h interval between two fractions on the same day or on Saturday. Total treatment duration (including planned/unplanned interruptions) is to be documented in days. Any patient must be available for intent to treat analysis.

Instead of the classical portal arrangements and dose distributions intensity modulated radiotherapy using an inverse calculation algorithm may be used in experienced centers. Dose constraints for normal tissues are at the discretion of the participating centers. Dose specification according to the RTOG protocol H 0022 is recommended. Details are given in a standard operation procedure.

Follow-Up Recruitment phase will be 4 years with physical examination, ECOG index, and quality of life questionnaire will be performed 3, 6 and 12 months after end of radiation. Further follow up will be performed annually up to 5 years to obtain sufficient clinical data.

Randomization and Sample Size The present study setup consists of a two armed randomized controlled trial (RCT) as primary study aim. Patients rejecting their participation to a randomized approach and preference to a certain procedure (radiation/no radiation) will be included into a prospective observational study after given informed consent. This parallel constructed observational trial will be performed with a maximum of

consistency to treatment
and observation compared to the RCT. In case of positive attendance the patients will be
randomized, stratified by the criteria of adequate lymph node therapy (yes/no) as formulated
by the DOESAK. Randomization to both groups (radiation group/control group) will be 1 to1.
Patients will be recruited over a period of 4 years and follow-up will be annually until the
trial ends, i.e. at least for 5 years for each patient. Sample size calculation will be
performed for the two-sided log rank test at a significance level of 5%. Assuming an
exponential distributed survival with survival probabilities after 5 years of 45% within the
control group and of 55% within the radiation group (results observed from the DOESAK
collective) and a drop-out rate of 5% per year, 280 patients per group are required to
detect a significant difference in overall survival with a power of 70%. In case of impaired
patient recruitment within the randomized trial, it is intended to recruit at least 280
patients per group in the observational study.

Analysis of RCT and observational trial

Initiation of this trial is only arguable with a realistic chance of statistical evaluation
of an adequate count of randomized patients. Hence an intermediate assessment of attendance
to randomization will be performed after the first and the second year of recruitment. If
less than 5% of patients agreed to randomization within the first and 10% within the second
year RCT will be stopped and the study is continued solely as observational trial (see table
1). Intermediate assessment is performed with presumption of accelerating involvement to
achieve a minimum of 20% randomized patients after the recruitment phase. As consequence to
the study design two different collectives (randomized collective/ collective with preferred
form of therapy) will exist. The following scenarios of analysis are possible:

1. If a sufficient number of patients was randomized, treatment comparison will be
performed within the randomized collective. The non-randomized collective will be used
to evaluate the external validity of observed treatment effects.

2. If no sufficient number of patients could be randomized, all recruited patients will be
analyzed. Descriptive comparison of treatment groups will be performed for all baseline

variables. All analyses will be performed with adjustment to baseline variables affecting survival. Results have to be interpreted with respect to any group differences in baseline variables.

Outcome measurements Primary clinical endpoint Overall survival Secondary clinical endpoints
Incidence of tumor relapse

- **Time to occurrence of lymphatic metastases**
- **Time to occurrence of local relapse**
- **Time to occurrence of distant metastases**
- **Tumor related death due to local tumor progression or metastatic spread**

Life quality

- **Time to provisional orofacial rehabilitation**
- **Time from operation to first intermediate prosthesis intake**
- **Time from operation to definitive prosthesis application**
- **Life Quality report (EORTC QLQ-C30 with H&N 35 module)**

Overall survival will be evaluated in a Cox proportional hazard model with treatment and adequate lymph node therapy (yes/no) as covariates. Further covariates may be considered if they affect survival.

Do you plan to share individual participant data with other researchers?

[---]*

Description IPD sharing plan

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Organizational Data

- DRKS-ID: **DRKS00005506**
- Date of Registration in DRKS: **2013/12/06**
- Date of Registration in Partner Registry or other Primary Registry: **2009/08/24**
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **[---]***
- (leading) Ethics Committee Nr.: **[---]***

Secondary IDs

- Primary Registry-ID: **NCT00964977 (ClinicalTrials.gov)**
- Sponsor-ID: **DOESAK-pN1-108399 (Johannes Gutenberg University Mainz)**

Health condition or Problem studied

- Free text: **Oropharyngeal Cancer**
- Free text: **Oral Cancer**
- Free text: **Lymph Node Metastasis**
- ICD10: **C10 - Malignant neoplasm of oropharynx**
- ICD10: **C00-C14 - Malignant neoplasms of lip, oral cavity and pharynx**
- ICD10: **C77 - Secondary and unspecified malignant neoplasm of lymph nodes**

Interventions/Observational Groups

- Arm 1: **Radiation: Radiation therapy**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Active control (effective treament of control group), Control group receives no treatment**
- Purpose: **Treatment**
- Assignment: **Parallel**
- Phase: **III**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **[---]***

Primary Outcome

- Primary study object: overall survival; time frame: 9 years; The objective of the clinical study will be to investigate two different patient groups (irradiated/unirradiated) with pT1/2 primary and verification of a singular ipsilateral lymph node metastasis in parallel design in order to evaluate the possible benefit of radiation therapy. The following null hypothesis forms the

basis of the present study: Radiation therapy will have no influence on the overall survival in patients with pT1/2, pN1 primary tumor. First patients will be observed for 9 years, last patient in will be followed-up for 5 years.

Secondary Outcome

- Time to occurrence of local relapse; time frame: 2, 3 and 6 months; 1 year to 9 years; Recruitment phase will be 4 years and follow up 5 years. First patients will be observed following the schedule above for 9 nine years, last patients will be observed for a minimum of 5 years.
- Time to lymphatic metastasis; time frame: 2, 3 and 6 months, 1 year to 9 years; Recruitment phase will be 4 years and follow up 5 years. First patients will be observed following the schedule above for 9 nine years, last patients will be observed for a minimum of 5 years.
- Time to occurence of distant metastasis; time frame: 2,3,6 months and 1 year to 9 years annually; Recruitment phase will be 4 years and follow up 5 years. First patients will be observed following the schedule above for 9 nine years, last patients will be observed for a minimum of 5 years.
- Quality of Life; time frame: after 6 months, 1 year and annually till end of study; QLQ 30 and HN35 Questionnaire will be assessed after 6 months and annually Course of provisional and definite orofacial rehabilitation will be assessed in each meeting

Countries of recruitment

- DE **Germany**
- NL **Netherlands**
- CH **Switzerland**

Locations of Recruitment

- **Universiätsklinikum Tübingen, Tübingen**
- **Universitätsklinikum Erlangen, Erlangen**
- **Universitätsklinik München, München**
- **Universität Regensburg, Regensburg**
- **Johann-Wolfgang Goethe-Universität, Frankfurt am Main**
- **Universitätsklinik Greifswald, Greifswald**
- **Universitätsklinikum Dortmund, Dortmund**
- **Universitätsklinikum Köln, Köln**
- **Department of Oral and Maxillofacial Surgery,, Mainz**
- **Otto von Guericke Universität Magdeburg, Magdeburg**
- **Universitätsklinik Rostock, Rostock**

- **Friedrich Schiller Universität Jena, Jena**
- **Universtiätsklinikum Aachen, Aachen**
- **Klinikum Augsburg, Augsburg**
- **Helios Kliniken Bad Saarow, Bad Saarow**
- **Charité Berlin, Berlin**
- **Universitätsklinikum Bonn, Bonn**
- **Klinikum Bremen-Mitte, Bremen**
- **Klinikum Bremerhaven, Bremerhaven**
- **Universitätsklinikum Dresden, Dresden**
- **Universitätsklinikum Düsseldorf, Düsseldorf**
- **Universitätsklinikum Essen, Essen**
- **Klinikum Frankfurt Oder, Frankfurt/Oder**
- **Universitätsklinikum Freiburg, Freiburg**
- **Klinikum Fulda, Fulda**
- **Marienhospital Gelsenkirchen, Gelsenkirchen**
- **Justus Liebig Universtität, Gießen**
- **Kreiskrankenhaus Gummersbach, Gummersbach**
- **Georg August Universitätsklinikum Göttingen, Göttingen**
- **Universitätsklinik Hamburg Eppendorf, Hamburg**
- **Medizinische Hochschule Hannover, Hannover**
- **Ruprecht-Karls-Universität Heidelberg, Heidelberg**
- **Universitätsklinikum Homburg/Saar, Homburg/Saar**
- **Universitätsklinikum Kiel, Kiel**
- **Bundeswehrkrankenhaus Koblenz, Koblenz**
- **Universitätsklinikum Leipzig, Leipzig**
- **Universitätsklinikum Schleswig-Holstein / Campus Lübeck, Lübeck**
- **Universitätsklinikum Mannheim, Mannheim**
- **Universitätsklinikum Marburg, Marburg**
- **Kliniken Maria Hilf Mönchengladbach, Mönchengladbach**
- **Universitätsklinikum Münster, Münster**
- **Brüderkrankenhaus St. Josef Paderborn, Paderborn**
- **Helios Kliniken Schwerin, Schwerin**

- **Klinikum Traunstein, Traunstein**
- **Universitätsklinikum Ulm, Ulm**
- **Helios Klinik Wuppertal, Wuppertal**
- **Universitätsklinikum Würzburg, Würzburg**

Recruitment

- Planned/Actual: **[---]***
- (Anticipated or Actual) Date of First Enrollment: **2009/10/31**
- Target Sample Size: **560**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **International**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

- histological diagnosis of a primary squamous cell carcinoma of the oral cavity or the oropharynx

- maximum tumor diameter less than 4 cm in the pathohistological specimen irrespective of histological grading (pT1 or pT2)

- concomitant histological verification of a singular ipsilateral lymph node metastasis less than 3cm in diameter (pN1) without penetration of the lymph node´s capsule and without presence of invasion of lymphatic vessels (lymphangiosis carcinomatosa)

- radical resection of the tumor within adequate resection margins (R0)

- written informed consent from the patient

- adequate performance status ECOG Index ≤ 2

Exclusion criteria

- an age less than 18 years old

- pregnant women

- reported drug addiction

- intake of remedies with potential influence on compliance or impaired judgment

- patients with mental disorders or conceivable physical, familial or job related embarrassments which may preclude the patient to realize the study schedule

- inadequate performance status ECOG Index > 2

Addresses

- **Primary Sponsor**

  Johannes Gutenberg University Mainz

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Sources of Monetary or Material Support

- **[---]***

Bitte wenden Sie sich an den Sponsor / Please refer to primary sponsor

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

Status

- Recruitment Status: **Recruiting ongoing**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

- Further trial documents **Homepage Deutsche Krebshilfe**
- Further trial documents **Study Homepage**
- Further trial documents **Moergel M, Jahn-Eimermacher A, Krummenauer F, Reichert TE, Wagner W, Wendt TG, Werner JA, Al-Nawas B. Effectiveness of adjuvant radiotherapy in patients with oropharyngeal and floor of mouth squamous cell carcinoma and concomitant histological verification of singular ipsilateral cervical lymph node metastasis (pN1-state)--a prospective multicenter randomized controlled clinical trial using a comprehensive cohort design. Trials. 2009 Dec 23;10:118.; 20028566**

The parameters in ClinicalTrials.gov and DRKS are not identical. Therefore the data import from ClinicalTrials.gov required adjustments. For full details please see the DRKS FAQs.
- Translation on version: 3
- Last processed date by ClinicalTrials.gov: 2013/12/01
Please note:
There are additional attributes available concerning this trial. To open an extended view please click here.