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Study protocol

Adenoid cystic Carcinoma and Carbon ion Only irradiation

ACCO-study

- prospective, open, randomized, two-armed, phase II study -

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0.0 Abbreviations

Abbreviation	
ACC	Adenoid cystic carcinomas
ALARA	As low as reasonable achievable
BED	Biologically Effective Dose
BfS	Bundesamt für Strahlenschutz (Federal Office for Radiation Protection)
C12 ion	carbon ions
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	clinical target volume
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FU	follow up
Fx	fractionation
GTV	Gross tumor volume
HIMAC	Heavy-Ion Medical Accelerator
HIT	Heidelberg Ion Beam Therapy Center
IMRT	intensity-modulated radiotherapy
KI	Karnofsky performance index
LC	local control
LEM	Local Effect Model
LET	linear energy transfer
MIT	Marburg Ion Beam Therapy Center
MRI	Magnetic Resonance Imaging
PI	principal investigator
QLQ-C30	Quality of life questionnaires - general
QLQ-H&N35	Quality of life questionnaires - head and neck
RBE	Relative biological effectiveness
RECIST	Response Evaluation Criteria in Solid Tumors
SOBP	spreadout Bragg peak
TD	Total dose
tox	toxicity

1.0 Synopsis

ACCO-study synopsis	
Titel	Adenoid cystic Carcinoma and Carbon ion Only irradiation
Acronym	ACCO
Prinicipal Investigator	Prof. Dr. Klaus Herfarth Dept. of Radiation Oncology University of Heidelberg
Study Coordinator	Dr. Sebastian Adeberg Dept. of Radiation Oncology University of Heidelberg
Study Statistician	Prof. Dr. Meinhard Kieser Institute for Medical Biometry and Informatics University of Heidelberg
Study Phase/Type	Prospective open phase II / Investigator-Initiated study
Planned Start of Study	Q4 2018
End of Study	Last patient in: Q4/2025
	Last patient out: Q4/2030
Study Objectives	Loco-regional control rate after 5 years
Design of Study	Monocentric open, prospective, randomized two-armed phase II study
Planned Patient Number	314 patients

Inclusion Criteria	• Histologically confirmed adenoid cystic carcinoma in the head and neck area
	• Indication for irradiation:
	  ○ non-operable and/or
	  ○ R1 / R2 resected and/or
	  ○ Perineural sheath invasion (Pn +) and/or
	  ○ pT3 / pT4
	• Informed consent
	• KI > 60% or ECOG 0/1 (minimum: self-sufficiency, normal activity or work not possible)
	• Age 18-80 years

ACCO-study synopsis	
Exclusion Criteria	• Rejection of study participation by the patient • Patient is not able to consent • Stage IV (distant metastases), with exception of pulmonary metastases of ≤ 1 cm • Lymph node involvement (clinical or pathological) • Previous radiotherapy in the head and neck area • Active medical implants for which there is no authorization for ion irradiation at the time of treatment (e.g., cardiac pacemaker, defibrillator, ...) • Contraindication to MR imaging • Simultaneous participation in another clinical study that could influence the outcome of this study or the other study
Description of Therapy	Loco-regional radiotherapy with carbon ions (C12) (experimental arm) versus photon IMRT + C12-Boost (control arm)
Definition of Target Volume	Primary tumor region with clinical safety margin considering the perineural spreading path
Organs at Risk	Brainstem, spinal cord, inner ear, temporal poles, optic chiasm, optic nerves on both sides, eyeball, lens, lacrimal gland, temporomandibular joints, Gll. parotis, Gll. submandibularis
Planned Study Duration per Patient	Irradiation planning: 2 weeks Duration of irradiation: ~4 weeks (22 fractions) experimental arm ~6 weeks (33 fractions) control arm Follow-up: 60 months from start of irradiation
Conduct of Study	Ion beam therapy centers of the University Hospital Heidelberg in Marburg or Heidelberg. The treatment is carried out on an outpatient basis.
Checkliste before Start of Therapy	• Informed consent for study participation • Current MR imaging incl. T1 / T2 Fat-Sat images (not older than 2 months) • CT Chest (not older than 3 months) • CT / sonography liver (not older than 3 months) • Bone scintigraphy • medical history and medical findings (weight, height, Karnofsky performance index) • Quality of life questionnaires QLQ-C30 and QLQ-H&N35 • Tooth reconstruction and fabrication of a fluoridation splint for irradiations in the jaw area • randomization
Examinations during Radiotherapy	Documentation of clinical symptoms and toxicities (according to the NCI CTCAE version 4.0 criteria)

ACCO-study synopsis	
Follow-up Examinations	6 weeks after the end of irradiation, then 6 months after the start of treatment and further every 6 months in the first two years, annually in the 3rd to 5th year Follow-up includes clinical findings, MRI, toxicity and quality of life, CT chest (once a year starting from follow-up month 12)
Primary Objective Criteria	Local-regional control rate after 5 years
Secondary Objective Criteria	Progression-free survival (5 years) Overall survival (5 years) Acute toxicity (CTC AE V4.0) Late toxicity (CTC AE V4.0) Quality of life (QLQ-C30 and QLQ-H&N35)
Study Population	The ITT population includes all randomized patients who are evaluated in the treatment arm to which they have been randomized. The ITT population is the primary scoring collective for all efficacy endpoints and patient characteristics. Per-protocol population (PP): All patients in the ITT population who have received the planned therapy in full and whose documentation is at least as complete as possible to derive conclusions about efficacy from the data. Analyzes of PP populations serve as sensitivity analyzes to investigate the robustness of the results from the ITT population. Safety population: All patients in the ITT population who have started the planned therapy (at least 1 day). Patients in the safety population are evaluated in the treatment arm they have been treated for. This is the primary evaluation collective for all safety endpoints.

ACCO-study synopsis	
Biometrical Methods	The primary objective of the study is to demonstrate that the local control rate 5 years after locoregional radiotherapy with C12 ions π_C12 is greater than the local control rate of bimodal radiotherapy π_bim. The null hypothesis (H0: π_C12≤π_bim; "the local control rate 5 years after locoregional radiotherapy with C12 ions is less than or equal to the local control rate in bimodal radiotherapy") is tested at the unilateral level α = 0.15, for the alternative of a local control rate 5 years after locoregional radiotherapy with C12 ions of π_C12 = 70% and in bimodal radiotherapy of π_bim = 60% (power of 0.75). For this purpose, a case number of 266 patients (133 per arm) is necessary using a Chi² test. Assuming a drop-out rate of 15%, 314 patients will be included in the study. The primary endpoint "locoregional tumor control according to MRI imaging after 5 years" is evaluated by means of a logistic regression model which is adjusted for the factors "residual tumor present" (yes / no) and "lung metastases present" (yes / no). In addition, the associated odds ratio for the treatment effect is given with a two-sided 70% confidence interval, missing values of the primary endpoint are replaced by multiple imputation, and the minor outcome criteria are evaluated using descriptive data analysis methods. In addition to specifying appropriate summary measures of the empirical distribution, descriptive two-sided 95% confidence intervals are given.
End of Study	The study ends with the follow-up visit at month 60 after inclusion of the last patient.

2.0 Summary

Adenoid cystic tumors are rare tumors of the head and neck region. Despite their slow growth, re-irradiation is often necessary due to the high metastatic risk. Patients are usually irradiated with photons or, as here at the Heidelberg University Hospital, with a combination of carbon ions and photons (bimodal radiotherapy). So far, there is no data from Europe available for the sole irradiation with carbon ions. The present ACCO (Adenoid Cystic Carcinoma and Carbon ion Only irradiation) study, a prospective, open-label, phase II, two-armed, randomized, investigator-initiated study, will therefore investigate the sole radiotherapy of carbon ions compared to bimodal radiotherapy in this tumor entity. Irradiation is applied in about 4 weeks (22 fractions); in a significantly shorter interval than the combination therapy (6 weeks, 33 fractions). Patients are followed up for further 5 years after the start of therapy. Carbon ions alone are expected to increase local tumor control rates from 60% to 70% after 5 years (primary objective criterion of this study). In order to reject the null hypothesis with a power of 75% and a one-sided significance level of α=15%, 314 patients are included (including a drop-out rate of 15%). Secondary objective criteria are progression-free survival, overall survival, acute and late toxicity, and quality of life.

3.0 Background

Adenoid cystic carcinomas are rare tumors (incidence 0.14 - 0.64 / 100,000), which occur mostly in the head and neck region (large and small salivary glands, nasal mucosa) and account for about 10-15% of malignant salivary gland tumors. They grow slowly; however, due to their growth pattern exhibit a tendency for local recurrences. For this reason postoperative irradiation is indicated, especially in the presence of risk factors (pT3 / 4, R1 / 2, Pn1). Lymphocytic metastasis is detected in 19% of salivary gland ACCs (GROUP 2017). The lymphocytic metastasis rate in ACCs of the nasopharynx, paranasal sinuses, lacrimal glands, or external auditory canal is only 5% (GROUP 2016). The most common hematogenous metastasis occurs in the lungs with an incidence of 35-50% (Bradley 2004). Other sites of metastasis are liver and bone. Patients with lung metastases can live asymptomatic for a relatively long time with the local control of the primary tumor being crucial for quality of life; while overall survival of patients with bone and liver metastases decreases significantly (median 54 months to median 20 months; (Sung, Kim et al. 2003)).

3.1 Radiotherapy with photons

Due to the rarity of ACC, reports of these tumors are usually retrospective analyses by individual clinics or institutes, extending over a very long period of time with changing radiation technology. Our own experience using modern photon techniques with a median dose of 66 Gy (single dose 1.8 - 2 Gy) resulted in a local control rate of 56% after 3 years and 40% after 5 years in 37 patients (Jensen, Nikoghosyan et al. 2015). 30% of the patients had an acute grade 3 toxicity of the mucosae. Higher-grade late radiation effects were reported in only 3% (hearing impairment) (Jensen, Nikoghosyan et al. 2015). Mendenhall and colleagues reported a local control rate of 77% after 5 years. However, in primary-irradiated (non-operated) patients, the control rate dropped to 56% (Mendenhall, Morris et al. 2004).

3.2 Radiotherapy with neutrons

Neutrons belong to the ion beams with a high linear energy transfer (high-LET). For a long time, adenoid cystic carcinomas were considered as the prime example for neutron irradiation as they the best control rates. In a South African series of 108 patients with ACC and macroscopic (residual) tumor, the 5-year local control was 52% (Stannard, Vernimmen et al. 2013). At dkfz, 29 patients with macroscopic ACC were treated with neutrons. The 5-year local control rate was 75%. The main problem of neutron irradiation are the late complications. In an

analysis of 335 neutron-treated salivary gland tumors, the actuarial risk of grade 3 or grade 4 complications was 20% (Stannard, Vernimmen et al. 2013). 17% of dkfz patients also exhibited late grade 3/4 toxicities.

3.3 Radiotherap y with combined modality (IMRT + C12)

Since 1997, our clinic collected data on combined irradiation with IMRT photons including the first draining lymph node area and a carbon ion boost of 6-8 fractions with 3 Gy (RBE) single doses. Initial data on this combined modality was published by Schulz-Ertner et. al. in 2005 and showed an advantage compared to the department's historical IMRT technique alone (Schulz-Ertner, Nikoghosyan et al. 2005). In 2015, this data was updated by Jensen et al. and extended with all patients who had received ion boost irradiation from the Gesellschaft für Schwerionenforschung (GSI) Darmstadt by the year 2007 (Jensen, Nikoghosyan et al. 2015): The 58 patients (all with macroscopic (residual) tumor) who received a combined therapy showed a progression free survival of 84% at 3 years and 60% after 5 years, at a median follow-up time of 74 months. This was significantly better than the historical comparison of 37 patients treated with a single IMRT (median follow-up 63 months, local PFS 3 years 59%, 5 years 40%). This benefit is also reflected in a significant survival benefit: median overall survival in the combination treatment is 102 months versus 74 months after IMRT alone ($p = 0.015$) (Jensen, Nikoghosyan et al. 2015). The COSMIC trial examined this methodology in a prospective fashion enrolling 53 patients with malignant salivary gland tumors (Jensen, Nikoghosyan et al. 2010). ACC histology was present in 47 patients (89%) and 33 patients (62%) had macroscopic (residual) tumor. With a median follow-up of 42 months, the local progression-free survival of ACC patients was 82% at 3 years, thus confirming the retrospective data from the previously mentioned GSI collective (Jensen, Nikoghosyan et al., 2015).
The toxicity of this combination treatment was not a limiting factor: In the COSMIC trial, reported severe grade 3 toxicities (> grade 2) were grade 3 mucositis in 25% of patients and grade 3 dermatitis in 10% of patients (Jensen, Nikoghosyan et al. 2015). In one patient, a higher grade late complication occurred (a carotid hemorrhage). In the GSI collective, late complications were a unilateral hearing loss in 10% of patients, a loss of smelling in 10% of patients and a unilateral blindness due to retinal detachment in one patient (2%) (Jensen, Nikoghosyan et al. 2015).
Due to the results of the GSI collective and the COSMIC study, bimodal therapy can be regarded as standard therapy.

3.4 Radiotherapy with carbon ions

Data for the sole treatment with carbon ions of ACC are from Japan. All treatments were done with passive beam modulation. To calculate the biological dose, dose profiles were performed assuming a fixed spreadout Bragg peak (SOBP). This system differs from GSI's local effect model (LEM) for C12 irradiation with active scanning. Conversion tables are used to compare the biological calculated doses (RBE_{HIMAC} vs. RBE_{LEM}) (Steinstrater, Grun et al., 2012). In addition, the irradiation in Japan was carried out with 3-4 fractions per week.
Mizoe et al. published data on dose escalation in a group of salivary gland tumors, of which 68% had ACC histology (Mizoe, Tsujii et al., 2004). The dose was increased from 18 x 2.7 Gy (RBE_{HIMAC}) to 18 x 3.9 Gy (RBE_{HIMAC}) with 3 exposures per week. In a later group, this was increased to 16 fractions (4x / week) with 3.3 - 4.0 Gy (RBE_{HIMAC}). The local control rates of these two groups did not differ significantly, reaching 75% at 3 years, 65% at 4 years and 60% at 5 years. Late toxicities > grade 2 on the mucous membranes was described in only one patient (3%). This patient developed a late toxicity > grade 2.
In a later series of 113 ACC patients, 16 fractions of 3.7 - 4.0 Gy (RBE_{HIMAC}) were administered (Ikawa, Koto et al.). Here, 3, 4, 5-year local control rates of 89%, 82% and 69% were achieved. 37

patients (33%) exhibited acute grade 3 toxicities of the mucous membranes. Late radiation effects ≥ grade 3 were reported in 27 patients (24%) (grade 3: cataract (10), osteoradionecrosis (7), brain necrosis (2), glaucoma (2), vision deterioration (2), mucosal ulcer (2); grade 4: Brain necrosis (3), blindness (5)).

Table: Japanese ACC studies with sole C12 irradiation:

Author	n	Single dose (SD) [Gy(RBE_{HIMAC})]	Fx	Total dose [Gy(RBE_{HIMAC})]	Corresponds SD [Gy (RBE_{LEM})]	BED 2 Gy (α/β=3.5)	5 yrs LC [%]	Late tox ≥3
Ikawa (Ikawa, Koto et al.)	113	3.7-4.0	16	57.6 – 64.0	4.2 – 4.4	92 - 101	69%	24%
Mizoe (Mizoe, Tsujii et al. 2004)	17	2.7 – 3.9	18	48.6 – 70.2	3.0 – 3.9	64 - 94	75%	0%
Mizoe (Mizoe, Tsujii et al. 2004)	19	3.3 – 4.0	16	52.8 – 64.0	3.7 – 4.4	87 - 101	50%	0%

The University Hospital of Heidelberg has gained experience with sole C12 ions irradiation in the recurrence situation after previous irradiation (Jensen, Poulakis et al. 2015): 52 patients previously irradiated with a median dose of 66 Gy (20 -115 Gy) were re-irradiated using carbon ions. The median dose was 51 Gy (RBE) in 17 fractions. Third-degree cerebral radiation necrosis occurred in 2 patients (4%), a third-degree dysphagia in 1 patient (2%), and 2 patients suffered grade 4 carotid haemorrhages at a median follow-up of 14 months. The rate of serious late complications was 6.5%. In particular, carotid haemorrhages are most likely due to the very high cumulative dose of the previous and current radiation (150 Gy and 180 Gy). The local tumor control was - pursuant to the lower radiation dose in the re-irradiation situation - at only 70% after 1 year (Jensen, Poulakis et al. 2015).

4.0 Study objectives

4.1 Primary Objective

- Loco-regional tumor control according to MR imaging after 5 years

4.2 Secondary Objective

- Progression-free survival after 3 and 5 years
- Overall survival after 3 and 5 years
- Acute toxicities according to NCI CTC AE (Version 4.0) during and up to 6 weeks after radiotherapy (rate of toxicity > 2 grade)
- Late toxicities according to NCI CTC AE (Version 4.0) from 6 weeks after radiotherapy (rate of toxicity > 2 grade)

5.0 Study Design

Prospective, open, two-armed, randomized, phase II study

6.0 Participating investigators/ study centers

The study performed as a monocentric study. The center for this study is:

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The center has two locations, the Heidelberg Ion Beam Therapy Center (HIT) and the Marburg Ion Beam Therapy Center (MIT). Patients will be recruited and treated at both locations.
Head of the clinical study for radiotherapy is Prof. Dr. med. Klaus Herfarth, Department of Radiation Oncology and Radiotherapy, University of Heidelberg.
The study coordination is carried out by Dr. med. Sebastian Adeberg, Department of Radiation Oncology and Radiotherapy, University of Heidelberg.
Additional physicians are the physicians at the Heidelberg Ion Beam Therapy Center (HIT) and Marburg Ion Beam Therapy Center (MIT) at the Department of Radiation Oncology and Radiotherapy at the University of Heidelberg.
Biometric planning is carried out by Prof. Dr. med. Meinhard Kieser, Institute of Medical Biometry and Informatics, University of Heidelberg.

7.0 Selection of Patients

7.1 Inclusion Crite ria

- Histologically confirmed adenoid cystic carcinoma in the head and neck area
- Indication for irradiation:
- non-operable and/or
- R1/R2 resected and/or
- perineural sheat invasion (Pn+) and/or
- pT3/pT4
- Informed consent
- KI > 60% or ECOG 0/1 (minimum: self-sufficiency, normal activity or work not possible)
- Age 18-80 years

7.2 Exclusion Criteria

- rejection of the study by the patient
- Patient is not able to consent
- Stage IV (distant metastases)
- lymph node involvement (clinical or pathological), with exception of pulmonary metastases of ≤ 1 cm
- Previous radiotherapy in the head and neck area
- Active medical implants for which there is no ion radiation authorization at the time of treatment (e.g., cardiac pacemaker, defibrillator, ...)
- Indication to MR imaging
- Simultaneous participation in another clinical study that could influence the outcome of this study or the other study

8.0 Patient registration

The study center keeps a logbook in which all patients who meet the selection criteria are recorded consecutively and documented in a registration form. If not included in the study, the reason is documented. All patients who fulfill the selection criteria, who have been informed and have given their consent to participate in the study, are registered as recruited at the study center and will be randomized subsequently. For this purpose, the registration form and the signed informed consent are handed over or faxed to the study center. In the study center, the registration form is checked for completeness and the patient is recorded in the logbook.
The informed consent of each patient takes place through a conversation between the study physician and the patient before inclusion in the study. The physician has to give the patient sufficient time for reflection and opportunity for further inquiries and must be convinced that the informed consent was understood by the patient. All questions of the patient must be answered and any ambiguities eliminated. The consent of the patient must explicitly refer to the collection and processing of personal data. Therefore, patients are explicitly informed about the purpose and scope of the survey and the use of this data, in particular health data. The storage of full names, dates of birth, addresses, and telephone numbers in the study center will be recorded in writing.
The patient may withdraw consent at any time and without giving any reason and discontinue the study. In such a case, he should be asked to give the reason for the termination, but pointed out that he does not have to do this.

9.0 Treatment planning

- Screening of the patient, indication
- Informed consent of the patient
- Randomization
- Acquisition of the medical history and medical findings (Karnofsky performance index, height, weight)
- Quality of life assessment (QLQ-C30 and QLQ-H&N35)
- Current MR imaging incl. T1 / T2 Fat-Sat images (not older than 2 months)
- CT Chest (not older than 3 months)
- CT / sonography liver (not older than 3 months)
- Bone scintigraphy
- Tooth reconstruction and fabrication of a fluoridation splint for irradiation in the jaw area

9.1 Radiation therapy

Radiation therapy is performed at the Heidelberg Ion Beam Therapy Center and at the Marburg Ion Beam Therapy Center using carbon ions alone (experimental arm) or using bimodal radiotherapy (control arm). In the experimental arm, a total of 22 fractions are administered in about 4 weeks (5-6 fractions per week). This corresponds to a significant reduction of the treatment time compared to the standard arm (33 fractions in about 6 weeks). The relative biologically effective dose is calculated from the physical dose using LEM1 and an alpha/beta value of 2.

9.2 Treatment planning

The patient is immobilized by the use of a thermoplastic mask. Computed tomography must be performed without contrast enhancement in 3 mm layers and if possible also with contrast medium.

9.3 Contouring

The following structures should be contoured:

Targets experimental arm :

GTV	Macroscopic tumor extension according to MRI at the time of treatment planning
GTVinit	initial GTV: preoperative tumor in operated patients
CTV_BP	GTV and possibly GTVinit plus 6 mm margin (9 mm along the perineural spreading path), considering anatomical boundaries
CTV_GP	CTV_BP plus 6 mm margin (12 mm along the perineural spreading path), considering anatomical boundaries; thereby partially included lymph node stations should be included completely

Targets control arm :

GTV	Macroscopic tumor extension according to MRI at the time of treatment planning
GTVinit	initial GTV: preoperative tumor in operated patients
CTV_BP	GTV and possibly GTVinit plus 6 mm margin (9 mm along the perineural spreading path), considering anatomical boundaries
CTV_GP	CTV_BP plus 3 mm margin and draining lymph nodes (level II and III only), in case of crossing the mid line, bilateral

Risk structures :

- brainstem
- spinal cord
- inner ear
- temporal pole
- chiasma opticum
- optic nerve on both sides
- eyeball
- lens
- lacrimal gland
- temporomandibular joints
- Gll. parotis
- Gll. Submandibularis

9.4 Dose prescription

The aim of optimizing the treatment plan is to achieve an as homogeneous and conformal dose distribution and maximum protection of the organs at risk as possible. The maximum exposure of the organs at risk should not exceed the TD 5/5 (toxic dose that causes 5% serious complications in 5 years) of the respective organs. The protection of spinal cord, chiasm and brain stem is a high

priority. The preservation of the respective optic nerves should be accomplished according to the initial tumor spread in consultation with the patient.

Table 1: The dosages refer to 95% of the volume. For carbon ions, the biological dose is based on the local effect model (LEM) 1, taking into account an alpha/beta value of 2 for all tissues.

	Experimental arm C12-only RT		Control arm Bimodal RT (p hoton s&C12)	
	CTV_GP	CTV_BP	CTV_GP	CTV_BP
Single dose	3 Gy(RBE)	3 Gy(RBE)	2 Gy	3 Gy(RBE)
Total dose	51 Gy(RBE)	15 Gy(RBE)	50 Gy	24 Gy (RBE)
BED2Gy*	61 Gy	18 Gy	50 Gy	29 Gy

* The equivalent dose BED2Gy is the dose corresponding to the applied dose in conventional fractionation (i.e., 2 Gy single dose, calculated with an α/β = 3 Gy for ACC).

9.5 Organs at risk

When complying with the tolerance doses, the fractionation effect must be taken into account in case of different partial exposure in the basic plan and boost plan. Here, the reference dose of 2 Gy and an α/β = 2 Gy applies to the organs at risk.

Table 2: Tolerance doses for organs at risk.

	TD / Isodose experimental arm	BED2Gy*	Comment
Brain stem	54 Gy(RBE) / 82%	60 Gy	Maximum surface
Optic chiasma	49.5 Gy(RBE) / 75%	52.6 Gy	Maximum
Optic nerves**	49.5 Gy(RBE) / 75%	52.6 Gy	Maximum
Spinal cord	45 Gy(RBE) / 68%	45.3 Gy	Maximum
Parotid gland****	31 Gy(RBE) / 47%	26.4	Mean Dose
Mandible bone	60 Gy(RBE) / 90%	69.8 Gy	Maximum surface
Lens***	ALARA		
Bulb***	ALARA		
Lacrimal gland***	ALARA		
[illegible]*	ALARA		
Temporomandibular joint***	ALARA		

* The values listed here also apply to the bimodal therapy, using an alpha / beta of 3 for the respective risk organs.
** Higher doses possible, after documented consultation with the patient that he accepts blindness of the respective side for achieving higher tumor control probability.
*** ALARA = As low as reasonable achievable
**** if not part of the target volume (e.g. contralateral side)

9.6 Controls at the irradiation device

The correct patient position during C12 irradiation is checked by means of daily orthogonal X-ray imaging and corrected if necessary. The irradiation in the control arm is performed as IMRT with image control, whereby the frequency of the image control can be determined individually depending on positioning inaccuracy and adjacent risk structure.

9.7 Supportive measures during radiation therapy

Radiation therapy is performed under outpatient conditions, inpatient admission for supportive therapy is possible at all times.
For target volumes with dose administration in the oral region or of the oro- or hypopharynx, supportive therapy with oral rinsing, Amphomoronal and Glandosane is recommended.

10.0 Clinical examinations (visits)

10.1 Overview

Clinical visits and content correspond to those of standard therapy. Study-related additional (time) effort results from the regular completion of the quality of life questionnaires (about 15 minutes per visit).

	IE	FE	FU week 6	FU month 6	FU month 12	FU month 18	FU month 24	FU month 36	FU month 48	FU month 60
In-/exclusion criteria fulfilled	x									
Informed consent	x									
Medical history/findings	x[a]		x	x	x	x	x	x	x	x
Karnofsky performance index	x		x	x	x	x	x	x	x	x
Height	x									
Weight	x		x	x	x	x	x	x	x	x
QLQ-C30 and QLQ-H&N35	x	x	x	x	x	x	x	x	x	x
Symptomes/Toxicities CTC AE	x	x	x	x	x	x	x	x	x	x
Documentation staging examin.	x[b]									
MRI	x[c]		x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]
CT chest	x[d]				x		x	x	x	x
CT/Sonography Liver	x[d]									
Bone scintigraphy	x									
Scheduling FU		x								

IE: Initial examination; FE: final examination of RT; FU: follow up; [a] incl. report and histology of surgery; [b] staging examination of chest, liver, bone; MRI head/neck; [c] less than 2 months old; [d] less than 3 months old; [e] including documentation of the remission status (remission, stable disease, progress)

10.2 Initial examination

- Medical history (incl. report and histology of surgery)
- Documentation of staging examination (chest, liver, bones, MRI head/neck)
- Assessment of quality of life (EORTC QLQ-C30 and QLQ-H&N35)
- Assessment of symptoms according to NCI CTC AE (version 4.0) criteria

10.3 Final examination

On the last day of irradiation (+/- 1 day) the final examination takes place with the investigator:

- Evaluation and documentation of toxicity
- Quality of life assessment using EORTC QLQ-C30 and QLQ-H&N35
- Scheduling of further follow-up appointments

10.4 Follow up

The oncological follow-up begins 6 weeks after the end of radiotherapy. Further follow-up appointments take place after 6, 12, 18, 24, 36, 48 and 60 months.
The following parameters are documented:

- Clinical status incl. Karnofsky performance index, weight
- Documentation of toxicities according to CTC AE 4.0
- MRI head/neck with remission status (remission, stable disease, progress)
- Quality of life assessment using EORTC QLQ-C30 and QLQ-H&N35
- CT chest (annually)

11.0 Duration of study participation

Patients are recruited over a period of 7 years. The evaluation of the study results regarding the primary endpoint of the study (locoregional control), takes place 60 months after the start of irradiation of the last patient. The end of the study is defined as the end of the follow-up period of the last patient (60 months after the start of treatment).
The planned start of the study is the fourth quarter of 2018.

first patient in	last patient in	last patient out
Q4/2018	Q4/2025	Q2/2030

11.1 Premature withdrawal of patients from the study

Individual termination criteria during the treatment phase:

- at any time at the request of the patient
- occurrence of therapy-resistant severe side effects (CTC grade 4 toxicity, which does not recover spontaneously, after supportive therapy or after a radiation break)

Individual termination criteria during the follow-up phase:

- at any time at the request of the patient

- tumor recurrence

Further procedures after termination:
In addition to the radiotherapeutic care for the documentation of late toxicities; toxicities are also recorded after completion of the study-related follow-up phase in cooperation with the supervising head and neck surgeon (only with the consent of the patient).

12.0 Assessment of efficacy

12.1 Timeline

Submission of the complete protocol for review in the Ethics Committee and the Bundesamt für Strahlenschutz is scheduled for the first quarter of 2018. Recruitment start is scheduled for the fourth quarter of 2018. With a recruitment of about 45 patients per year, the fourth quarter of 2025 is aimed for as end of the recruitment.

12.2 Definition of relapse

A direct implementation of the RECIST criteria on the Response Evaluation is often not possible due to the growth behavior of the frequently occurring radiogenic changes in the irradiated area. The response evaluation is therefore primarily descriptive. A recurrence suspicion should be validated in a second examination 2-3 months later.

13.0 Safety

13.1 Assessment of Safety

The acute and late toxicities of radiotherapy are based on the NCI CTCAE Version 4.0 criteria and are recorded during and after therapy continuously at the respective follow-up appointments.

Grade 1 = mild (no therapeutic measures required)
Grade 2 = moderate (outpatient drug therapy)
Grade 3 = difficult (inpatient therapy)
Grade 4 = life-threatening or leading to disabilities
Grade 5 = side effect with lethal consequences

Typical toxicities and their classifications according to CTC AE V4 are listed in the appendix of the protocol.

13.2 Data Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will monitor recruitment, reported adverse events and data quality at least once a year. Based on its report, the DSMB will make recommendations to the principal investigator regarding the modification, continuation or termination of the study. The DSMB consists of independent experts in the field of radiation oncology (Prof. Dr. Marc Münter, Klinikum Stuttgart and Prof. Dr. Florian Sterzing, Strahlentherapie Süd, Kempten). The mission of the DSMB will be to ensure the ethical conduct of the study, as well as the protection of safety interests of the patients in the study. Problems that are identified will be discussed with the PI who will take appropriate action. Relevant information (including relevant [illegible] is included in the status reports of the study, which serves as a base of discussion for the study team sessions in which the PI, the study coordinator and sub-investigators participate.

14.0 Duration of the study /study withdrawal

4.1 Regular end of study

Regular end of the treatment phase: 4 weeks after the start of radiotherapy (C12 irradiation only); 6 weeks after the start of radiotherapy (bimodal radiotherapy)
Regular end of study participation: after a follow-up period of 5 years

14.2 Premature end of trial/ Withdrawal of the whole study

Reasons for premature termination of the entire study are:

- Decision including benefit-risk assessments of the study management when unacceptable risks and toxicities occur
- Consideration of termination for each grade 5 toxicity, 2 consecutive grade 4 toxicities, 5 consecutive grade 3 toxicities
- new (scientific) evidence during the study
- Inadequate recruitment rate

14.3 Individual criteria for withdrawal

- serious event during the radiation phase (grade 4 or 5 toxicity)
- Withdrawal of the patient's consent to study participation

15.0 Biometrics

15.1 Sample size calculation

The primary objective of the study is to demonstrate that the local control rate 5 years after locoregional radiotherapy with C12 ions π_C12 is greater than the local control rate of bimodal radiotherapy π_bim. Control rates of approximately 60% were observed with treatment with IMRT and C12 Boost and it is estimated that this rate could be improved by 10% under C12 (see chapter 3.4). The null hypothesis (H0: $\pi_{C12} \leq \pi_{bim}$; "the local control rate after 5 years in locoregional radiotherapy with C12 ions is less than or equal to the local control rate in bimodal radiotherapy") is tested at the unilateral level $\alpha = 0.15$, for the alternative of a local control rate 5 years after locoregional radiotherapy with C12 ions of $\pi_{C12} = 70\%$ and in bimodal radiotherapy of $\pi_{bim} = 60\%$ (power of 0.75). For this purpose, a number of 266 patients (133 per arm) is necessary using a Chi² test. Assuming a drop-out rate of 15%, 314 patients will be included in the study. Evaluation by means of a logistic regression model, which is adjusted for the factors "residual tumor present" and "lung metastases present", an increased power is expected due to the additionally explained variance. Missing values are to be replaced by multiple imputation (see Section 15.4), which is also to be expected to increase power. The calculations were done with nQuery Advisor version 7.0.

15.2 Randomization

Successively screened and eligible patients will be included in the study after study start. To obtain comparable treatment groups (experimental group: locoregional radiotherapy with C12 ions, control group: bimodal radiotherapy) with respect to known ("residual tumor presence" (yes / no) and "lung metastases present" (yes / no)) and unknown risk factors, each patient becomes randomized to the treatment groups in balanced permutated blocks and stratified for residual tumor and lung metastases using the web-based software randomizer.at (by the Institute of Medical Informatics, Statistics and Documentation of the Medical University of Graz (https://www.randomizer.at) provided). 314 patients will be randomized.

15.3 Study Population

The ITT population includes all randomized patients who are evaluated in the treatment arm to which they have been randomized. The ITT population is the primary scoring collective for all efficacy endpoints and patient characteristics.
Per-protocol population (PP): All patients in the ITT population who have received the planned therapy in full and whose documentation is at least as complete as possible to derive conclusions about efficacy from the data. Analyzes of PP populations serve as sensitivity analyzes to investigate the robustness of the results from the ITT population.
Safety population: All patients in the ITT population who have started the planned therapy (at least 1 day). Patients in the safety population are evaluated in the treatment arm they have been treated for. This is the primary evaluation collective for all safety endpoints.

The assignment of each patient to the different analysis populations (ITT, PP, safety population) is defined and explained in detail in the statistical analysis plan.

15.2 Evaluation

The primary endpoint "locoregional tumor control according to MRI imaging after 5 years" is evaluated by means of a logistic regression model which is adjusted for the factors "residual tumor present" (yes / no) and "lung metastases present" (yes / no). The null hyposthesis is tested to the one-sided level of α = 0.15. The increased significance level compared to a confirmatory Phase II study on the one hand takes into account the phase II character of the study and, on the other hand, the number of patients that can be recruited in a manageable time frame with which a sufficiently high level of power can be achieved. In addition, the corresponding odds ratio for the treatment effect is given with a two-sided 70% confidence interval: Missing values of the primary endpoint are replaced by multiple imputation, using the "fully conditional specification" Method (van Buuren, 2007). The factors "treatment group" (experimental arm / control arm), "residual tumor present "(yes / no) and" lung metastases present "(yes / no)" will be accounted for in the imputation process. Sensitivity analyzes include a complete case analysis as well as a best and worst case analysis. In addition, the time-to-event curve for the main objective criterion is estimated using the Kaplan and Meier method (1958).

The study is supervised by an independent Data Safety Monitoring Board (DSMB), which assesses the benefit-risk profile of the studied therapy during the course of the study and, if necessary, informs the study management, if the DSMB considers changes to the study execution as necessary. The corresponding assessment and, if applicable, a resulting recommendation of the DSMB will be delivered to the principal investigator.

The secondary objective criteria are evaluated by methods of descriptive data analysis (Abt, 1987). Corresponding to the scaling level, suitable positional and scattered measures of the empirical distribution are specified for ordinal and interval-scaled variables. For nominally scaled endpoints, absolute and relative frequencies are calculated. For time-to-event endpoints, the Kaplan-Meier method estimates the probability of each target event occurring as a function of time. In addition, descriptive interpretive two-sided 95% confidence intervals - for time-to-event endpoints with adequate consideration of censored observations – will be calculated and reported. Further details of the evaluation are specified in a statistical analysis plan, which will be finalized before the database is closed. All calculations are done with SAS version 9.4 or higher.

16.0 Data management

16.1 Patient identification log

All patient-related data are recorded in a pseudonymised form. Each patient is uniquely identified by a patient identification number. The investigator maintains a patient identification list in which the patient identification numbers are associated with the full patient name. This list must be kept absolutely confidential and must not leave the testing center. The patient identification list must be archived for at least 15 years after the end of the study.

16.2 Data collection/ Case Report Forms

Data collection is based on case report forms. The sheets have to be filled in with a ballpoint pen. Entries in pencil or ink are not allowed. Corrections are to be carried out in the following way: The incorrect entry is crossed out with a simple line, the correct information is entered next to it and initialed by the investigator with the date and, if necessary, provided with the reason for the correction. Data fields which cannot be completed due to missing information must be commented on.
The CRFs should be completed without delay and then should be checked by the investigator, signed with the date and sent to the study center.

16.3 Archiving of Essential Documents

The originals of all crucial study documents, including CRFs, are kept in the study center for at least 15 years after the final report has been prepared.
The principal investigator of the study center keeps the administrative documents (correspondence with the ethics committee, study administration, study center), the patient identification list, the signed declarations of consent, copies of the CRFs and the general study documentation (protocol, amendments) for the above mentioned time.
Original data of the patients (medical records) must be kept for the required archiving period of the study center, but not less than 15 years.

16.4 Data protection

Personal data (full name, date of birth, address) and data on the treatment and the course of the disease (medical findings, types of treatment, prescribed medication, etc.) from the study participants will be collected. These data are subject to medical confidentiality and the provisions of the Bundesdatenschutzgesetzes (BDSG). They are electronically stored and evaluated in a pseudonymised* form using an unique identification number. Patient data will only be shared in a pseudonymised form. Third parties do not get any insight into original documents.
* Pseudonym means that only a number or letter code is used, possibly in combination with initials and the year of birth (not date of birth). A subsequent assignment of the samples / data to a specific person is only possible with the help of a "key" code, which is managed in the study center.

17.0 Ethical Aspects

17.1 Declaration of Helsinki

The study will be carried out in accordance with the ethical principles described in the applicable version of the Declaration of Helsinki.

17.2 Ethics Committee

The study protocol, patient information and the informed consent document are submitted to the ethics committee of the Medical Faculty of the University of Heidelberg. The study will begin only after receiving the approval vote. The Ethics Committee will be promptly informed by the principal investigator of any changes in the study protocol that may affect patient safety.

17.3 Subject information and informed consent

Before being admitted to the clinical study, the patient must consent to participate after being fully informed by the investigator or a designated member of the investigating team about the nature, importance, risks and individual consequences of the clinical study and their right, to terminate the participation at any time. The informed consent to participate in the clinical study may be withdrawn by the patient verbally in the presence of, or in written form directed to, the investigator or a physician member of the investigating team at any time during the study. The patient must not entail any disadvantage or be coerced or unduly influenced to continue to participate. Furthermore, the patient is not obligated to disclose reasons for the withdrawal of the consent.

After reading the informed consent document, the patient must give consent in writing. The patient should also have the opportunity to consult the investigator, or a physician member of the investigating team about the details of the clinical study. The patient's consent must be confirmed by the personally dated signature of the patient and by the personally dated signature of the physician conducting the informed consent discussion.

17.4 Informed consent for irradiation

All patients will receive a separate information about the radiation procedure and will give their informed consent to irradiation. This information will specify the risks of the procedure according to the treatment site. The informed consent for the irradiation will be documented on the site specific head and neck forms and archived along with the radiation plan and radiation protocol.

17.5 Usage, storage and circulation of data

The rules on medical confidentiality and data protection will be respected. Patients are informed that their disease-related data are stored in pseudonymised form and used for scientific evaluations (publications, registration dossiers). Patients have the right to be informed about the stored data. An inspection of the original medical records by a third party is only carried out by the principal investigator or officials of competent supervisory authorities. Data managers are required to maintain strict confidentiality and privacy.
Upon withdrawal from the study, data already collected will be destroyed if the patient has not consented to further use of the data.

18.0 Legal and administrative aspects

18.1 GCP

This study complies with the recommendations of Good Clinical Practice (refer to ICH-GCP: International Conference on Harmonisation - Good Clinical Practice; 01.05.1996)

18.2 Legal aspects

The statutory requirements of the Radiation Protection Ordinance (Strahlenschutzverordnung, Bundesgesetzblatt 2001 Part I No. 38, dated 26.07.2001, last amended by Article 5 paragraph 7 of

the Law of 24.02.2012), the X-ray Ordinance (Röntgenverordnung) and the Directive on Radiation Protection (Richtlinie zum Strahlenschutz) are complied with.
The principal investigator has at least two years of experience in clinical trials.

18.3 Radiation protection and insurance

The study was reported to the Federal Office for Radiation Protection (Bundesamt für Strahlenschutz; BfS). The BfS confirmed application of radiotherapy in the experimental arm on the 24.09.2018. The BfS will be informed about the amendment of the 24.09.2018, which includes randomization against a control arm. A radiation protection insurance will be completed for the patients (insurer: HDI-Gerling Industrie Versicherung AG, insurance number 57 010310 03018). Study-related radiation exposure will only be initiated once the required approvals have been obtained from the BfS. The permit requirement is based on the use of carbon ions. All radiological examinations for staging during the follow-up phase correspond to clinical routine.

18.4 Funding

The Radiology Department, Department of Radiology and Radiation Therapy, University Hospital Heidelberg, INF 400, 69120 Heidelberg, will cover the costs of the clinical study. The study will be submitted to the Deutsche Krebshilfe for funding. Personnel resources for the treating physicians, study nurses, the data management and project management are applied for. In addition, printing costs, travel expenses (for the DSMB and the exchange HIT / MIT), monitoring, the fees of the ethics committee and the Federal Office for Radiation Protection (Bundesamt für Strahlenschutz), as well as for the patient insurance are requested. Participation in the study will not cause any additional costs for patients (compared to the standard treatment). All persons involved (including the principal investigator and coordinator) declare that there is no conflict of interest in connection with the implementation and evaluation of the study.

18.5 Public ation

The results of the study will be published. The order of authorship is determined by the principal investigator.

18.6 Adherence to protocol and protocol amendments

The study protocol must be adhered to. Any deviation from the intended examination and treatment measures or dates for which the investigator or a physician member of the investigating team is responsible must be documented and justified (for example, emergency measures). Amendments or addendums to the study protocol can only be initiated and authorized by the principal investigator.

19.0 Literature

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20.0 Signature Page

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