Intraoperative verification of maxillary malignancy resection with cone-beam computed tomography

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PROTOCOL TITLE “Intraoperative verification of maxillary malignancy resection with cone-beam computed tomography”

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CBCT	**Cone-beam computed tomography**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
MRI	**Magnetic Resonance Imaging**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**(Serious) Adverse Event**
SMN	**Sinonasal malignant neoplasms**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Maxillary malignant neoplasms constitute a group of tumours that present often at an advanced stage. Their surgical management can therefore be challenging, regarding also their proximity to significant structures like the orbit and the brain. Particularly, cases with extensive disease and recurrent tumours are often incompletely resected and local treatment failure is commonly observed, ranging from 30% to 50%, according to the literature.

Objective: The primary objective of this study is to assess the feasibility of utilizing intraoperative cone-beam CT (CBCT) to verify the intended excision margins of maxillary malignant tumours. CBCT images will be matched with a preoperative planning of the resection margins on the preoperative MRI. This study will be the first step before conducting a randomised control study that will evaluate the efficacy of CBCT verified resection.

Study design: Exploratory pilot study.

Study population: A total number of 6 patients, above 18 years old, with maxillary cancer suitable for management with open maxillectomy will be included. All patients will undergo a pre-operative MRI scan of the maxilla for the evaluation of the local extent of the tumour. In this MRI, the tumour volume that is indented to be resected will be segmented.
The patients will be studied in two distinct phases:
1. Three patients will undergo the standard maxillectomy and intra-operative control with CBCT, however without any further resection

2. Three patients that will undergo the maxillectomy and intra-operative CBCT and additional excision, in case that residual tumour is observed based on the preoperative MR resection planning.

Main study parameters/endpoints: The main parameter of this pilot study is the technical success of implementing CBCT during maxillectomy as an additional tool for the control of the resection. Operating time will be recorded and the mean duration of the procedure will be calculated. Assessment of the possible residual tumour volume will be also performed based on the intraoperative CBCT, as well as comparison to the planned resection volume as calculated in the preoperative imaging planning. The quality of CBCT and MRI scan matching will also be evaluated. No correlation to clinicopathological parameters will be established in this study.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden for the individual patient is the extra operating time it takes (approximately 15 minutes for each CBCT scan). The only extra risk involves the additional

exposure to ionizing radiation, although the dose of a CBCT scan is significantly lower than that of a conventional CT of the head (approximately 1/3 to 1/6 of the dose). Open maxillectomy itself is a well-established, routine treatment modality used as a standard procedure in patients with maxillary malignancy. The potential benefits for the patients are also considerable. Till now the surgeon's experience in recognizing potential residual tumour is the main factor for a successful maxillectomy. The intra-operative use of CBCT can potentially verify the complete tumour resection, minimizing the risk of residual tumor and local treatment failure.

1. INTRODUCTION AND RATIONALE

Maxillary cancer

Maxillary malignant neoplasms are rare tumours with annual incidence rates around 1 per 100,000 in most developed countries. They represent less than 1% of all neoplasms and less than 10% of those arising in the head and neck region. Due to the contiguity of the nasal cavities with the paranasal sinuses, identifying the specific site of origin of large maxillary tumours is often difficult. Squamous cell carcinoma is the most common malignant tumour, followed by carcinomas of the minor salivary gland (e.g. adenocarcinoma, adenoid cystic carcinoma) and melanomas. A number of substances and occupational circumstances are correlated to maxillary cancer, including wood and leather dust, as well as chromium and nickel compounds. Rarely, tumours of mesenchymal origin, such as ossifying angiofibroma, chondrosarcoma and osteogenic sarcoma, arise in this region.

Imaging studies are essentially performed in cases of maxillary malignant tumours, providing information about the extent of the disease, potential contraindications to biopsy (intensely contrast-enhanced lesion), staging and treatment planning. The first line examination is computed tomography with bone and soft tissue windows and contrast injection. MRI can also suggest the diagnosis in the presence of a heterogeneous unilateral opacity. Biopsy of the suspected lesion confirms the final diagnosis.

Surgery is the mainstay of treatment for most cases of maxillary cancer. Radiation as the sole modality of treatment is recommended for unresectable cases and poor surgical candidates. Combination therapy of surgery and adjuvant radiotherapy with or without chemotherapy is given in situations with an advanced tumor (T3 and T4), positive surgical margins, perineural spread, perivascular invasion, cervical lymphatic metastasis, and in recurrent tumours. Majority of cases present at an advanced stage of disease, with a massive tumour size and invading surrounding bony structures and sinuses, leading to a high frequency of local failure, that ranges from 30% to 50%. This high rate of local failure is a significant factor of poor prognosis in cases of maxillary malignant tumours. Survival rates in large series vary, depending upon case mix. In general, overall survival rates around 50% have been reported.

Image-Guided Surgery

Image-guided surgery (IGS) is a broad field of research and clinical practice that utilizes a variety of visualization technologies – e.g., a rigid endoscope, fluoroscopy, CT and MRI images, and ultrasonography – to improve performance of surgeries that require high precision and accurate geometric information of the surrounding tissue. Image guidance systems were initially accepted by two main medical disciplines, neurosurgery, for which the technology was originally developed, and

orthopaedics. The main reason for the quick uptake of these surgical techniques is that both disciplines accommodate the rigid anatomy assumption on which the technology was developed. In neurosurgery the brain's motion is constrained by the skull, although brain shift is an issue, and in orthopedics the assumption is almost always valid. Current commercial applications carry forward this restriction, but application of IGS for deformable anatomical sites is the subject of investigation.

Ideally, modern IGS systems should augment and complement the ability of the surgeon to understand the spatial structure of the anatomy by integrating medical images and other sources of information, such as tracked instruments. Sindwani et al describe an ideal IGS system to:

- Be highly accurate, maintaining accuracy throughout the procedure
- Be physically unobtrusive, easily integrated into operating room
- Be user friendly
- Be inexpensive
- Be applicable for preoperative evaluation and surgical planning
- Allow seamless intranasal and external navigation with a variety of equipment
- Incorporate any existing images for navigation, avoiding repeat imaging
- Permit multimodal navigation (fusion technology)
- Allow intraoperative updates of preoperative image datasets
- Permit extended applications & robotic integration

Yavin et al describe these systems to give potentially a three-fold effect: (1)They can mitigate the learning curve for invasive procedures and reduce the variability of the outcome, narrowing the gap between exceptional and standard practice; (2) They may enable new minimally invasive procedures, allowing physicians to perform procedures that were previously considered high-risk and (3) They transform qualitative procedure evaluations into quantitative ones, enabling a quantitative comparison between plan and execution.

A branch of IGS, also known as computer-aided surgery or surgical navigation, allows the localization of interventional tools with respect to images acquired from various modalities, such as CT and MRI. These systems employ real-time tracking, either electromagnetic or optical, and provide feedback with visualization software. Such systems have demonstrated geometric accuracy of approximately 2 mm at the start of surgery and deteriorating by less than 1 mm by the end of the procedure, which is adequate for most operations involving rigid anatomy.

Image Guidance in Head and Neck Surgery

Anatomy related to head and neck surgical procedures includes both soft tissue structures – e.g. sinus mucosa and surrounding contents of the orbits and nasopharyngeal space – and rigid structures – e.g. the mandible, cribriform plate, and skull base. Surgical procedures in this region range from tumour ablation and neck dissection to endoscopic sinus surgery. Head and neck

surgery challenges arise due to infiltrative disease within complex anatomy surrounded by sensitive critical structures. This is compounded by large normal variations of anatomy, such as the sinus cells and clivus, and a high cost of damage to normal tissue, such as blindness (breach of optic nerves), bleeding (breach of carotid arteries), and cerebrospinal fluid leak (breach of central nervous system via the cribriform plate or clivus). Critical structures pertaining to head and neck surgeries are illustrated in Figure 1.

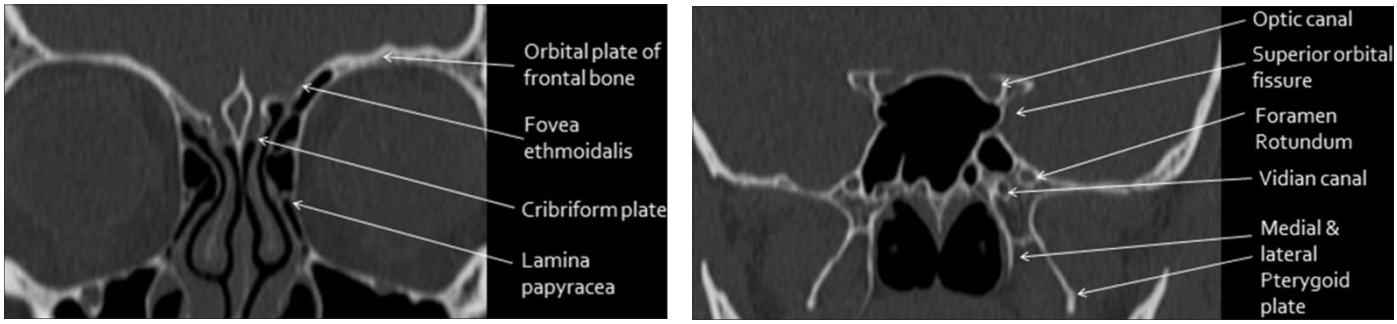

Figure 1. Critical structures surrounding the paranasal sinuses as demonstrated in coronal CT scans of nose and paranasal sinuses.

Performance in head and neck surgery can be limited by the availability of accurate geometric information to the surgeon. The uncertainty that arises can result in incomplete excision of the disease – e.g. in less than half of the cases, the tumour excised with open or endoscopic surgery. The need for accurate image based guidance through precise images is clear. Image guided surgery has found application in head and neck surgery, where accurate, high precision image-guidance helps avoid complications that may arise due to the numerous sensitive critical structures and can increase completeness of the procedure. Image guided surgery has been explored in many head and neck procedures ranging from the paranasal sinuses and frontal recess to skull base and temporal bone surgeries. According to the literature, intraoperative CBCT has been used as an imaging tool during the surgical management of facial fractures, orthognathic and temporal bone surgery, in addition to surgical performance studies of endoscopic sinus surgery in cadavers. There is only one feasibility study about the implementation of CBCT in a limited number of head and neck oncology cases (12 cases, including maxillectomy, mandibulectomy and craniofacial resection). According to this report, intraoperative CBCT demonstrated excellent spatial resolution and detailed bony definition, whereas soft tissue differentiation was rated as satisfactory. Nonetheless, data are lacking regarding the value of intraoperative CBCT in achieving tumour-free resection margins, and thus improving local disease control and prognosis in head and neck surgery.

The purpose of the current pilot study is to investigate the feasibility of CBCT imaging during open maxillectomy for malignant neoplasms. The next future step will be the implementation of this

imaging method in a prospective randomized control study, in which two groups of patients will be distinguished: the first group will be treated with maxillectomy using intraoperative CBCT and the second group will receive the conventional procedure without intraoperative imaging.

2. OBJECTIVES

Primary Objectives

Investigate the feasibility of intraoperative imaging with CBCT in open maxillectomy for verifying resection of the intended treatment volume.

Assess the feasibility of the intended treatment volume segmentation and resection planning based on the preoperative imaging.

3. STUDY DESIGN

This is a prospective study which has the character of an exploratory pilot study, establishing the implementation of CBCT in patients undergoing maxillectomy for malignant tumours. Patients with maxillary sinus malignancies are included irrespectively of histological type, first presentation of disease or recurrence, that will undergo open maxillectomy, as indicated. This applies to stages T1-T4a for non-melanomas (SCC, adenocarcinoma, adenoid-cystic carcinoma, etc) and T3-T4a for melanomas of the maxilla. All patients will undergo preoperative MRI and planning of the resection volume using the medical imaging processing software WorldMatch. There will be two phases in this study: 1. In the first phase, three patients will undergo the standard surgical procedure and control with intraoperative CBCT, without any further resection. 2.In the second phase, three patients will undergo the same procedure as in phase 1, but will receive additional excision if the CBCT reveals residual tissue that was included in the preoperative imaging planning.

4. STUDY POPULATION

4.1 Population (base)

Patients who are diagnosed with malignant maxillary tumours and are planned for open maxillectomy. All histopathologies are eligible.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Primary tumours of the maxilla (T1-T4a for non-melanomas and T3-T4a for melanomas), confirmed by biopsy. Recurrent cases are also eligible.
- Any lymph node status
- M0
- Treatment plan approved by the multidisciplinary head and neck oncology meeting of the AvL.
- Age over 18-years old
- No contraindications to general anesthesia
- Informed consent, written and signed

4.3 Exclusion criteria

- Unresectable tumours of the maxillary sinus
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol
- Pregnancy

4.4 Sample size calculation

As this is a pilot study, no power calculation on sample size has been performed. A total number of 6 patients is considered sufficient to be included, to observe and test the technical feasibility.

Preoperative imaging with MRI of the maxilla will be obtained for all patients. Segmentation of the resection area will be then performed on the coronal and transverse sections of the MRI scans of each patient using the imaging processing software WorldMatch. Two distinct phases, each one including 3 patients, will be further created:

- In the first phase, the patients will undergo the conventional open maxillectomy procedure and the intraoperative imaging with the CBCT. Comparison of the preoperative and intraoperative scans will be conducted, using imaging fusion of the MRI and the CBCT

scans. No further intervention will be applied to this group, independently of the result of the intraoperative imaging.

- In the second phase, the patients will also undergo the primary resection and the intraoperative imaging. However, if the comparison of the preoperative with the intraoperative imaging reveals residual tumour that is included in the preoperative imaging resection planning, then the surgical procedure will continue in order to excise the target tissue. In this case a second CBCT will be carried out to confirm the complete resection.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

All patients included in the study have disease that can be managed by open maxillectomy. In general, and depending on the extension of the tumour, different approaches can be used for an open maxillectomy. Common incisions include the lateral rhinotomy, the Weber-Ferguson incision or the modified Weber-Ferguson incision with a Lynch extension. The resection may include one of the following procedures:

- Medial maxillectomy: The extent of bone resection includes the inferior and middle turbinates and ethmoid air cells cephalad and to the floor of the nasal cavity caudad. It is indicated for well-differentiated or low-grade malignant tumours and other tumours of limited extent on the lateral wall of the nasal cavity or the medial wall of the maxillary antrum.
- Peroral partial maxillectomy (Infrastructure Maxillectomy): when the upper alveolar ridge or hard palate are involved.
- Subtotal maxillectomy: A subtotal maxillectomy essentially removes the entire maxilla except the floor of the orbit.
- Total Maxillectomy: Complete removal of the maxilla becomes necessary when a primary tumour arising from the surface lining of the maxillary sinus fills up the entire antrum. Primary mesenchymal tumours arising in the maxilla such as soft tissue and bone sarcomas also require total removal of the maxilla to encompass the entire lesion.
- Total Maxillectomy with Orbital Exenteration: A radical maxillectomy with orbital exenteration is indicated when a primary tumor of the nasal cavity or paranasal sinuses extends into the orbit through the orbital periosteum. Orbital exenteration of a functioning eye with normal vision is considered only if the possibility of a curative resection exists. Removal of a functioning eye for a palliative operation is not recommended.
- Total Maxillectomy with Orbital Exenteration and Reconstruction with Free Tissue Transfer.

After completion of the resection, intraoperative CBCT will be obtained. The patients included in the second phase of the study may receive further resection and a second CBCT scan to confirm that the intended treatment volume is resected.

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameters/endpoints

- Technical feasibility of determining and marking of the planned treatment volume in the preoperative MRI.
- Technical feasibility of obtaining intraoperative CBCT of the maxilla.
- Assessment of the quality of matching (CBCT and MRI) by using the “Sorensen-Dice coefficient” and “Hausdorff distance” (for the definition of these terms, see section 8.3-Comparison of preoperative and intraoperative imaging).
- Rate of complete resection achieved compared to the preoperatively planned treatment volume.

8.1.2 Secondary study parameters

Not applicable

8.2 Randomisation, blinding and treatment allocation

There is no randomization or blinding.

8.3 Study procedures

Preoperative segmentation of the resection area

Preoperative imaging with MRI of the paranasal sinuses will be obtained for all patients (standard clinical procedure). Delineation of the resection area will be then performed on the coronal and transverse sections of the MRI scans for each patient using the imaging processing software WorldMatch (See figure 2 for an example). The intended treatment volume is then automatically calculated. The preoperative segmentation process is performed by the head and neck surgeon (principal investigator) in collaboration with the radiologist. The intended resection volume will be saved for comparison with the CBCT images.

Surgical resection

The maxillectomy will be performed in the conventional manner. The surgeon who has examined the pre-operative MRI will remove the tumour to his best judgement without any intraoperative image guidance (i.e. navigation). The surgeon will aim to achieve removal of the pre-opertive intended treatment volume.

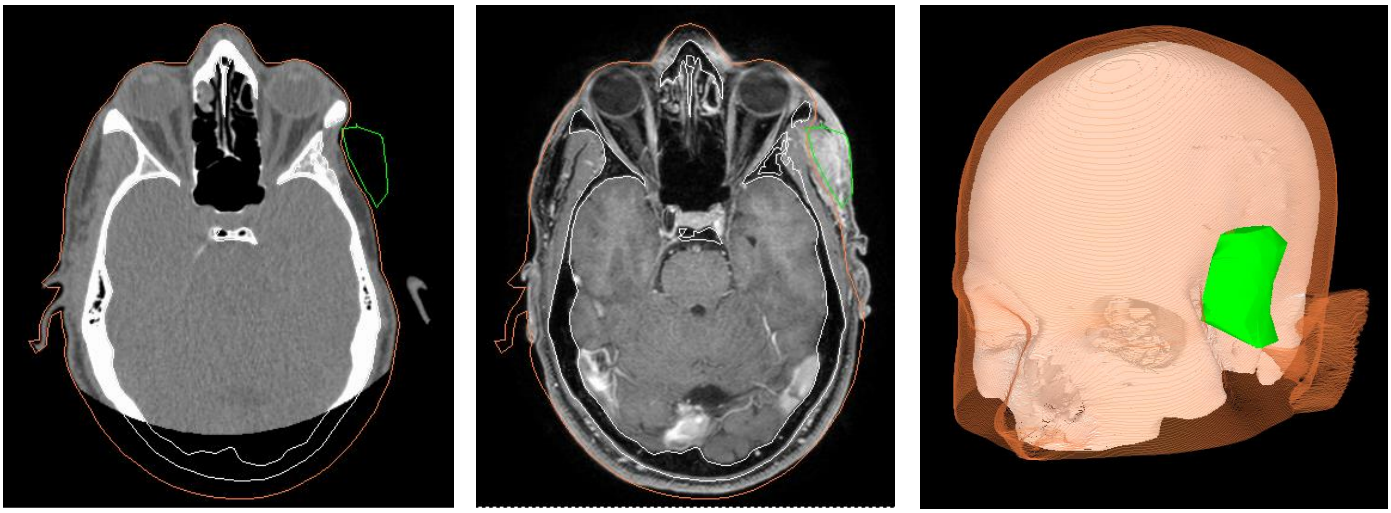

Figure 2: left: Post-operative CT scan. Middle: preoperative MRI-scan. Right: 3D rendering of the skull, skin and tumor. On the CT-scan the area of the tumor is visible in green and clearly demonstrates an adequate resection of the tumor area (green area is gone on the post-operative CT-scan).

Intraoperative CBCT scan

After completion of the tumour resection, evaluation of the margins with CBCT (Xpert, Allura FD20 developed by Philips) i.e. based on a mobile isocentric C-arm is performed. Intraoperative CBCT imaging is implemented such that it preserves sterility through covering the entire C-arm with custom made plastic sheets mend for this procedure and the placement of a transparent sterile drape over the patient during imaging.

The presence of metal objects in the surgical field and operating table can lead to deleterious streak artifacts in CT images; therefore, strategies for artifact management are incorporated, including the use of "CT-compatible" materials and removal of metallic objects from the x-ray field during imaging whenever possible. Anesthesia lines containing artifact-inducing metal (e.g., electrocardiogram [ECG] leads, temperature, and pulse-oximeter) are positioned outside of the imaging field when logistically feasible, while nonmetallic lines (e.g., blood pressure and ventilation tube) were positioned freely.

The exact timing of all intraoperative image acquisitions is at the discretion of the operating surgeon who initiates the imaging procedure by asking surgical staff to step back from the table and remove nonessential instruments from the operating field. At this time, the transparent, sterile drape is placed on the patient. The C-arm is moved to a position orthogonal to the table by the research staff. During image acquisition, an authorized x-ray technician and research staff member operate the C-arm from a computer control station positioned behind a lead-glass window located in the adjacent room. In accordance with as-low-as-reasonably-achievable principles of radiation protection, all other members of the operating team leave the room during imaging, and the remaining 2 to 3 in-room personnel behind the mobile shield wall wear lead aprons and thyroid shield collars. After image acquisition, the C-arm is withdrawn from bedside to a park position in the operating room to minimize interference with the standard surgical setup and workflow, and clinical staff returns to the room.

Intraoperative CBCT acquisition, according to the Allura, XperCT Head Protocol, consists of 621 images at 120 kV, involving rotation of the C-arm gantry from below ("nonsterile") to above ("sterile") the operating table. Radiation doses of 1.6 mSv are delivered, providing visualization of bony detail and soft tissue at doses sufficiently low for repeat intraoperative imaging (compared to a typical 2–5 mSv diagnostic head CT).

Comparison of preoperative and intraoperative imaging – evaluation of resection

Matching of the preoperative MRI (that includes the preoperatively segmented resection margins) with the intraoperative CBCT images is performed using the above mentioned imaging software WorldMatch.

- For the patients included in the first phase of the study, after the acquisition of the CBCT scans, the maxillectomy is terminated and the reconstruction of the maxilla follows according to the standard procedure. Preoperative and intraoperative imaging matching will be performed postoperatively. The matching procedure is based on the bony structures surrounding the tumor area on MRI and CBCT. The tumor area shown in MRI is expected to be occupied by air in the post-operative CBCT. Figure 3 summarizes the procedure followed for phase I patients.
- For the patients of the second phase, thorough evaluation of the matched images is performed by the head and neck surgeon, before the reconstruction of the maxilla. If the excision is fully accomplished according to the preoperative plan, then the resection procedure is terminated and the reconstruction of the maxilla follows. The surgical procedure will be continued, only in case that there is suspicious residual tumour, included in the imaging resection planning. The complementary tissue resection is limited at the level where the residual tumour is detected, based on anatomical landmarks. After the supplementary resection, a second CBCT is obtained, as described in the previous section, and the same fusion procedure with the preoperative imaging is repeated. This second imaging evaluation is used to confirm the additional excision of the residual tumour. No more than two CBCT scans will be performed. The whole procedure for phase II patients is summarized in Figure 4.

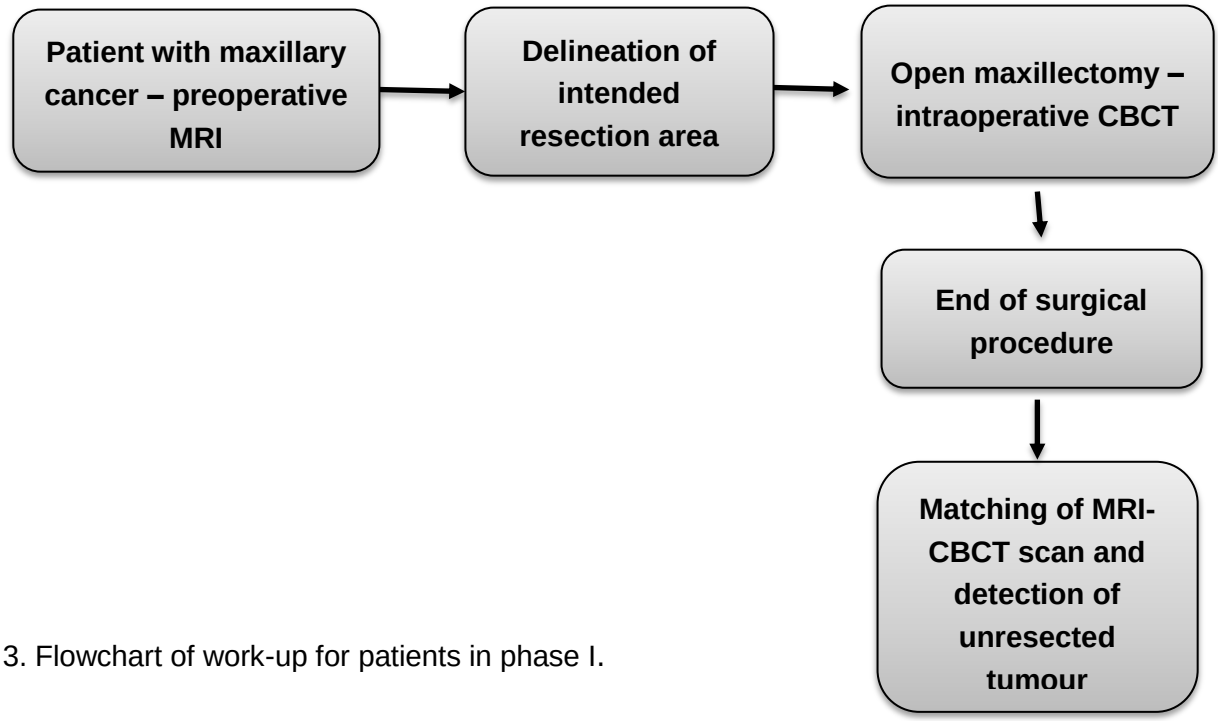

Figure 3. Flowchart of work-up for patients in phase I.

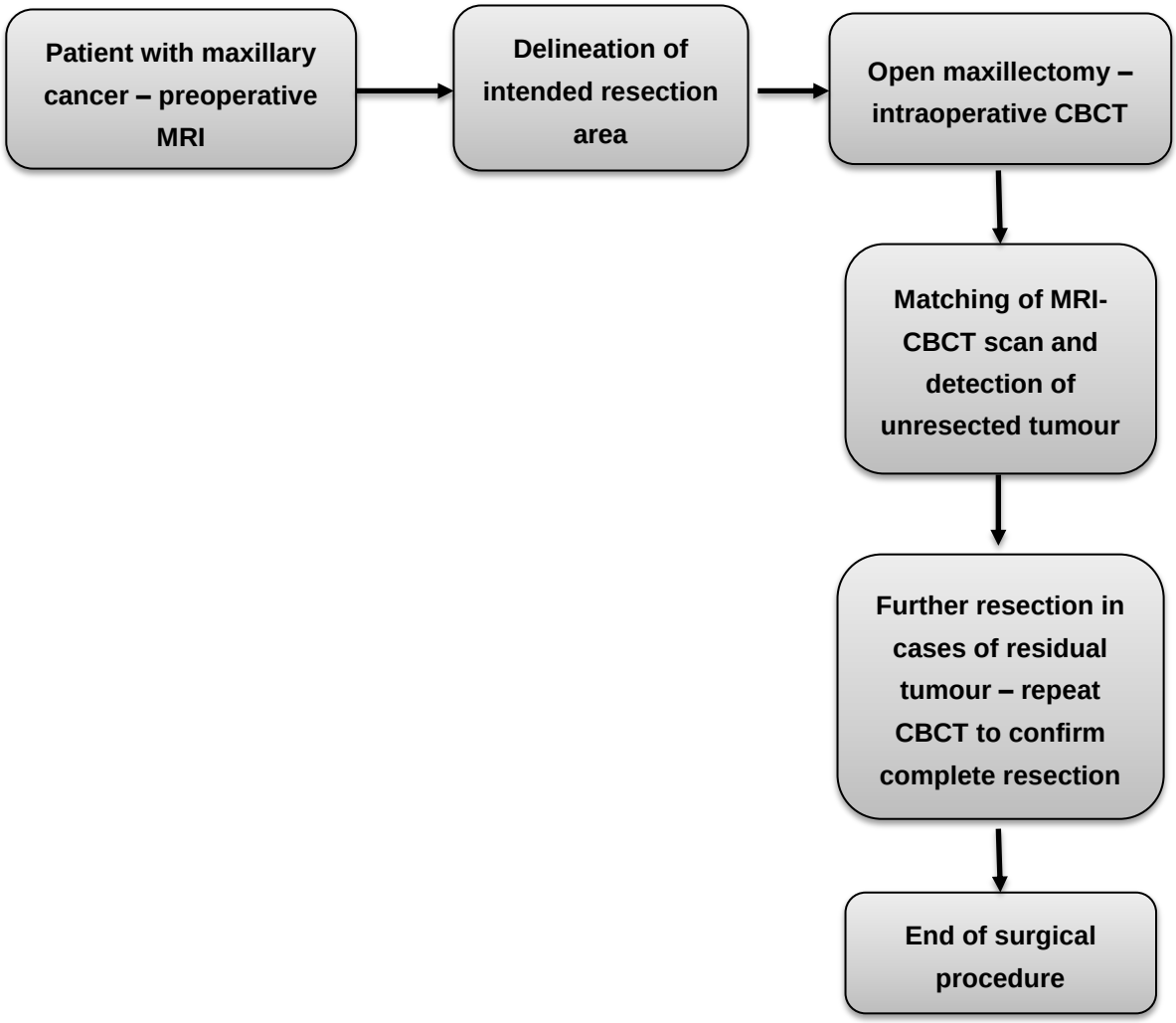

Figure 4. Flowchart of work-up for patients in phase II.

Quality assessment of the preoperative and intraoperative imaging matching will be performed using two indices:

- The *Sorensen-Dice coefficient* is a statistic used for comparing the similarity of two images. Sørensen's original formula was intended to be applied to presence/absence data, and is:

$$QS=\frac{2[A\cap B]}{[A]+[B]}$$

A and B represent, in this case, two distinct images that are superimposed on one another (Figure 5). The index ranges between 0 and 1, depending on how complete is the overlap between the two images (0: no overlap; 1: complete overlap).

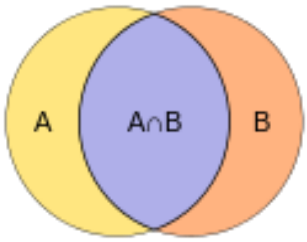

Figure 5. Two different images A and B, partially overlapping with each other.

- The *Hausdorff distance* is a metric between two point sets. It measures the extent to which each point of a set lies near some point of another set. Since an image can be considered as a set of points, Hausdorff distance can be used to determine the degree of resemblance of two images. The following formula is used to calculate the index, considering two different sets of points, A (including points a_1, a_2, a_3 etc) and B (including points b_1, b_2, b_3 etc):

$$H(A,B) = max(h(A,B), h(B,A))$$

where

$$h(A, B) = \max_{a \in A} d(a, B) \text{ and } d(a, B) = \min_{b \in B} \rho(a, b)$$

d(a, B) is the distance from a point a to the set B, and ρ(a, b) is a point distance in the metric space M.

Quality assessment of imaging matching will be performed after completion of the surgery.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time, for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.5 Replacement of individual subjects after withdrawal

After withdrawal of a subject, the principal investigator will decide for their replacement.

8.6 Follow-up of subjects withdrawn from treatment

Subjects that withdrew from the study will be followed up according to the normal, routine clinical procedures.

8.7 Premature termination of the study

Not expected

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs and SAEs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product / trial procedure/ the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3 Annual safety report

Not applicable

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached.
Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB)

Not applicable

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

The primary study parameter is to evaluate the feasibility of utilizing CBCT as an imaging tool for the intraoperative verification of the complete resection of maxillary malignant tumours. The mean time of the procedure, including imaging, will be calculated. Additionally, the residual tumour volume in the CBCT scans will be estimated, as well as the ratio to the planned resection volume in the preoperative MRI. Quality assessment of the CBCT and MRI matching will be performed using the “Sorensen-Dice coefficient” and the “Hausdorff distance”. Since this is a pilot study, no correlation to clinicopathological parameters will be performed.

10.2 Interim analysis

Not applicable

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (adopted during 59th WMA General Assembly, Seoul, October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

11.2 Recruitment and consent

All patients will be informed by their head and neck surgeon about the aims of the study, the possible adverse events, the procedures and possible hazards to which the patient will be exposed. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. Patients are asked to fill in and sign an informed consent form and return this to the principal investigator if they agree to participate in this study. The informed consent procedure is according to the ICH Guidelines on Good Clinical Practice. An example of the translated informed consent form is enclosed in appendix 1.
This protocol will be submitted for approval by the Medical Ethics Committee of the NKI-AvL before the study starts and patients can be included.

11.3 Objection by minors or incapacitated subjects

Not applicable

11.4 Benefits and risks assessment, group relatedness

The burden and risk is minimal, whereas the benefits are evident, not only for (future) patients, but also in general.
Burden:
The burden for the individual patient is the extra operating time it takes due to additional imaging procedure (approximately 15 minutes for each CBCT scan).

Risks:
Open maxillectomy is a well-established, routine treatment modality and the general risks are well known. The only extra risk involves the additional exposure to ionizing radiation, although the dose of a CBCT scan is significantly lower than that of a conventional CT of the head and neck.

Benefits:
For the patient: The surgeon's experience is a significant factor for complete tumor excision and, thus, for a successful maxillectomy. In this study, control of the resected area will be performed based on the comparison of the intraoperative CBCT with the preoperative imaging (MRI) planning. This way, complete tumour resection (according to imaging) will be confirmed. Resection free margins according to intraoperative imaging can potentially increase the possibility of pathologically free margins, which in turn is a major predictive factor of prolonged survival. Moreover, the use of imaging provides an additional tool for the control of the proximity to significant anatomical structures, and thus decreasing the complication rates.
Benefits in general: The use of CBCT suggests an innovative imaging technology that may have an important contribution in the radical excision of maxillary malignant tumours, affecting positively on the patients' prognosis. Thus, the current study may have a significant impact on the way the procedure is nowadays performed.

11.5 Compensation for injury

The sponsor has a liability insurance which is in accordance with article 7 of the WMO.
The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

All personal data will be handled confidentially. Data will be inputted into an Excel data form. The data form will be stored in the personal computer of the coordinating researcher. Access to the data will be allowed only to the researchers.
The handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: D e Wet Bescherming Persoonsgegevens, Wbp)

12.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.3 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.4 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.5 Public disclosure and publication policy

All information resulting from this trial is considered to be confidential, at least until appropriate analysis and study coordinators of the trial have completed checking.
Any publication, abstract or presentation comprising results from the trial must be submitted for examination and approval to study coordinators.

13.STRUCTURED RISK ANALYSIS

Not applicable

14. REFERENCES

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