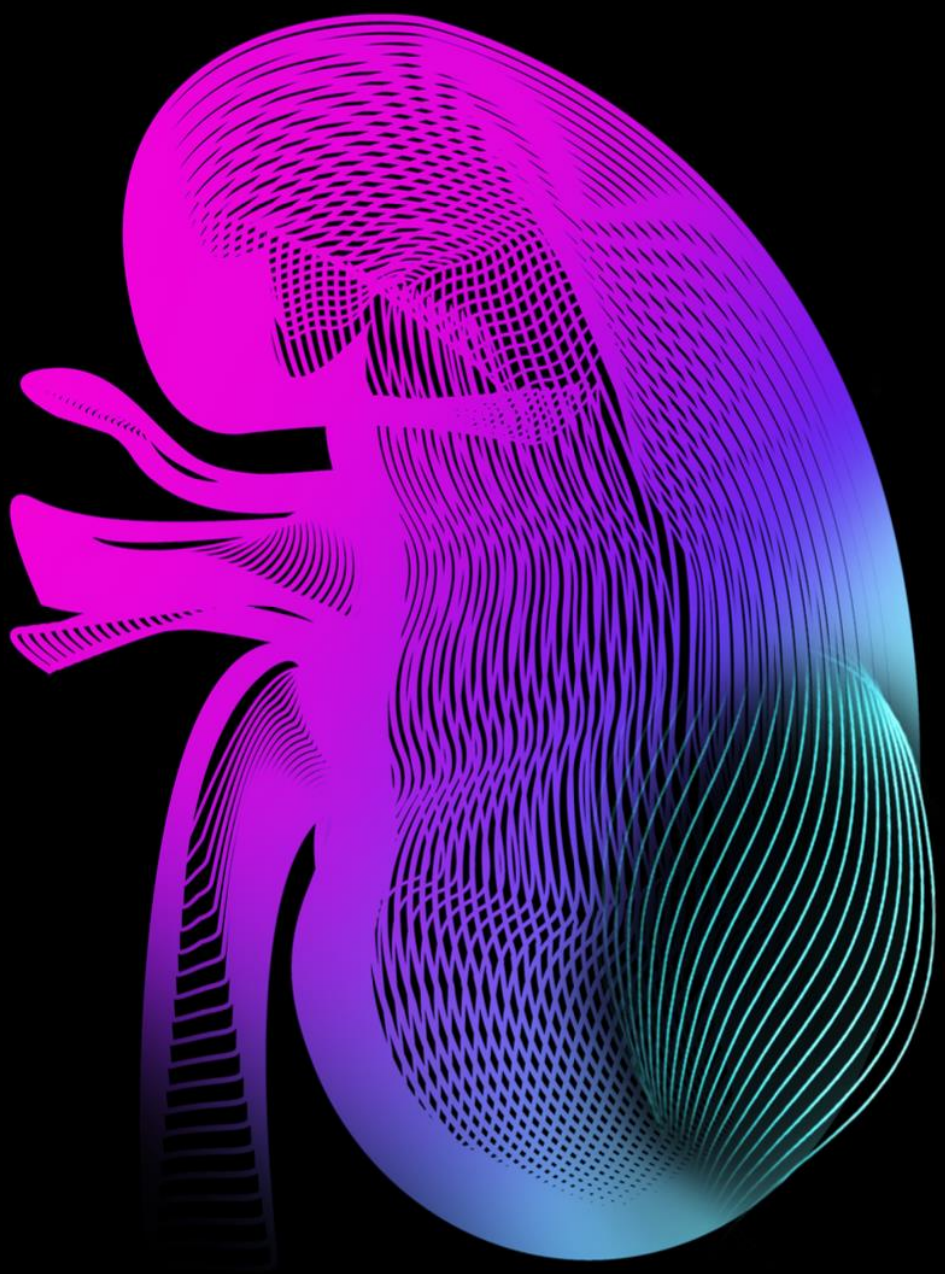
Introducing new dimensions in pediatric oncologic surgery

Matthijs Fitski



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Chapter 1 Introduction

This chapter outlines the clinical context and technical background of the research (section 1.1), and its purposes (section 1.2). Section 0 describes the scope of this research by summarizing the objectives. To finalize, an outline of the remaining chapters is given (section 1.4).

1.1 CLINICAL CONTEXT

Renal tumors are the second most common pediatric solid tumors with roughly 26 patients each year in the Netherlands (1). Wilms' tumor (WT) is the most common pediatric renal tumor and has an overall survival of roughly 90% (2). Pediatric patients with a renal tumor typically respond well to the given treatment, specifically patients with WT. In Europe, Asia and South America, patients are treated according to the International Society of Pediatric Oncology Renal Tumor Study Group (SIOP-RTSG) treatment protocol. Patients in North America follow the treatment protocol of the Renal Tumor Committee (RTC, formerly known as the National Wilms Tumor Study Group) of the Children's Oncology Group (COG). Although both protocols differ significantly, especially in the preoperative phase, the overall survival (OS) and event-free survival (EFS) are roughly similar. In the Princess Máxima Center, most patients follow the SIOP-RTSG 2016 UMBRELLA protocol. This protocol consists of neoadjuvant chemotherapy for most patients, surgical resection and adjuvant chemotherapy possibly combined with postoperative radiotherapy.

Diagnosis

Patients with a renal tumor are commonly referred to a hospital after unexpected palpation of an abdominal mass. Patients may present with fever, pain, hematuria, or hypertension. After abdominal ultrasound confirms a renal mass, the patient is referred to an expert center. Here the patient undergoes another abdominal ultrasound by a specialized pediatric radiologist to confirm a renal tumor. Directly thereafter the patient receives a diagnostic abdominal Magnetic Resonance Imaging (MRI) for further differentiation of the renal mass and to determine the extent of the disease. Possibly bilateral or multifocal disease is confirmed at this stage. Computed Tomography

(CT) of the thorax is used to determine the presence of pulmonary metastases. Furthermore, if present, the extent of a venous thrombus can be determined. Based on these findings, the patient receives four or six to twelve weeks of neoadjuvant chemotherapy. The goal of neoadjuvant chemotherapy is to shrink the tumor to facilitate less complicated surgery and reduce the chance of intraoperative tumor rupture.

A patient might be suspected for a predisposing syndrome. Currently, over 100 syndromes have been associated with WT (3). To confirm or disconfirm an underlying predisposing syndrome, all renal tumor patients are referred to a clinical geneticist for counselling (4). Predisposing syndromes are expected to be responsible for roughly 33% of the WT patients (5) (6). These patients with a predisposing syndrome typically have a higher chance of metachronous disease. Therefore, accurate diagnosis is crucial.

The diagnostic stage of the patient is based on imaging to determine the initial oncologic treatment plan. Preoperatively, patients with unilateral local disease receive four weeks of neoadjuvant actomyosin and vincristine (AV). Patients with metastatic disease receive six weeks of neoadjuvant AV combined with Doxorubicin. Bilateral patients receive three to twelve weeks of neoadjuvant AV followed by nephron-sparing surgery if deemed possible. In case of no response to treatment, treatment is switched to carboplatin and etoposide. It is allowed to prolong the period of neoadjuvant chemotherapy up to 12 weeks to spare the maximum potential of nephron for consequent preservation of kidney function.

Surgical treatment

After initial diagnosis and neoadjuvant chemotherapy, the tumor is surgically removed which is an essential part of treatment. In patients with nonsyndromic unilateral disease, removal of the complete kidney with tumor (total nephrectomy; TN) is the most common surgical approach. Alternatively, patients may require nephron-sparing surgery (NSS). During the latter, the surgeon aims to completely remove the tumor whilst also preserving as much healthy kidney parenchyma as possible (7). NSS is only performed in selective cases such as patients with bilateral disease and patients with an underlying predisposing syndrome. If the patient has bilateral disease, the surgeon will nearly always aim for NSS for all lesions or a combination of TN and NSS to avert kidney transplantation. This is highly undesirable for these young patients. For syndromic patients, NSS is also the surgical treatment of choice due to the increased risk of metachronous disease in the contralateral kidney (8). For these patients, when the initial tumor is

resected through a TN, a second tumor in the contralateral kidney necessitates NSS. Yet at this stage, this may not be technically feasible. Therefore, to ensure options for surgical treatment later in life, NSS is the preferred option for the initial tumor whenever feasible.

TN is considered safe and feasible for nonsyndromic unilateral Wilms' tumor patients (nsuWT). However, after TN, patients are expected to have a higher risk of chronic kidney disease later in life due to a higher blood pressure and decreased estimated Globular Filteration Rate (9–12). Moreover, surgical treatment options are limited for patients with a solitary kidney later in life. NSS has the possibility to overcome or reduce these problems. Yet NSS is only considered within the UMRBELLA treatment protocol for nsuWT patients if the tumor volume is <300 ml at diagnosis and if the tumor is restricted to the upper- or lower pole of the kidney or laterally around the mid-kidney. Also, a substantial amount of the healthy renal parenchyma should be spared. These oncological guidelines ensure precise evaluation of each individual case. This is important as NSS is considered very difficult, is only rarely performed, and increases the rate of surgical complications. In 13.3 – 36.4% of the cases treated with NSS, the surgeon did not completely remove the tumor. This complication is called a positive surgical margin. A positive surgical margin upstages the patient (Directly stage III) lowering the overall survival and thus necessitating additional chemotherapy and possibly radiotherapy. In most cases it is unknown where and how these positive surgical margins occurred making it difficult to prevent them.

Nevertheless, NSS has the potential to reduce long-term sequelae in patients with WT. To make NSS more accessible for our patients, we need to focus on two urgent matters. Firstly, the amount of positive surgical margins needs to be reduced through improvement of the surgical pre- and intraoperative approach. This requires further understanding of this complication and improvement of patient-specific anatomical understanding, which is discussed further in section 1.2 (13). Secondly, the surgical decision-making requires harmonization. This ensures less variation in the feasibility assessment of NSS in further international studies (14,15).

This debate of NSS for nsuWT patients is partially still ongoing due to a lack of harmonization of surgical guidelines. Currently, there are no surgical guidelines on how to assess the feasibility of NSS and the oncological guidelines may be insufficient for this assessment. Harel et al. give an excellent overview of this debate and how the criteria for surgical feasibility assessment creates differences in feasibility of NSS between multiple studies (16). These studies have been primarily performed under the COG-RTC treatment protocol and are therefore

difficult to translate to the SIOP-RTSG treatment protocol. Cost et al. postoperatively examined the feasibility of NSS on pathological specimen of 78 WT patients not receiving neoadjuvant chemotherapy (17). The feasibility of NSS was described through the following surgical criteria: unifocal mass outside of the hilar region, favorable histology, no invasion of the vasculature or renal sinus, no metastatic lymph nodes and a clear visual difference between renal parenchyma and tumor tissue. Based on these criteria, they estimate that roughly 24% of the patients could be eligible for NSS. In another study by the COG-RTC, Ferrer et al. used image-derived risk factors to determine the feasibility of NSS for 60 nsuWT patients (18). When comparing preoperative CT data with their developed guidelines, the reviewing committee consisting of an experienced NSS surgeon and radiologist only considered 8% of the patients feasible for NSS. Within SIOP, Wilde et al. reported their experience with NSS for uWT patients in 2014 (19). Out of 2800 uWT patients receiving preoperative chemotherapy, only 91 patients (3%) were surgically treated with NSS. This low number contributed to a strict adherence to the oncological guidelines within the SIOP WT-2001 study and surgical prudence with this relatively new surgical treatment. While showing a good OS and EFS after NSS similar to TN for patients without metastatic disease, they stress the necessity to perform a careful assessment when considering patients for NSS. No risk should be taken to ensure no upstaging the disease to stage III. Currently there is a clear difference between theoretical and actual patients eligible for NSS. To overcome this difference and for NSS to be considered for nsuWT patients more frequently, clearer surgical consensus for the feasibility assessment of NSS are required.

1.2 TECHNICAL BACKGROUND

Together with harmonization of the patient assessment prior to surgery, we also need to improve our intraoperative judgement. We believe that inaccurate understanding of the patient-specific anatomy by the surgeon may be contributing to positive surgical margins when performing NSS. As mentioned earlier, the goal of NSS is to completely remove the tumor while preserving functional kidney parenchyma. This requires accurate intraoperative localization of the tumor, both on the surface but also within the kidney. After localization, the surgeon determines a resection border in the healthy kidney around the expected tumor surface to ensure complete removal of the tumor. Intraoperative Ultrasound (ioUS) may be used to determine the depth of resection and find the surrounding vasculature and urine collection system. All this anatomical information needs to be interpreted and

combined with oncological surgical principles to determine a plan of resection. With this plan, the surgeon should always aim for en bloc resection, avoiding tumor spillage, a margin of healthy parenchyma around the tumor, all the while avoiding dissection of major vessels within the kidney and opening the urine collection system (15). If the surgeon misjudges, macroscopic tumor tissue may remain in the patient (a positive surgical margin) or (a part of) the kidney may be lost. Both have serious consequences for the patient, as mentioned in section 1.1.

To get a better understanding of this anatomical information and determine the plan of resection beforehand, surgeons prepare for surgery using medical imaging data. The surgeon determines the tumor location, amount of tumor infiltration and other anatomical relationships of the patient based on preoperative cross-sectional imaging such as CT or MRI. The surgeon interprets this preoperative imaging and translates it to the intraoperative situation. During the procedure, there are no adequate techniques to perform this translation. The ioUS supports the surgeon but is challenging to work with for a surgeon, especially during a stressful intraoperative situation. Recent advancements in image-guided surgery have led to new techniques to perform this translation of imaging with anatomy and pathology, aiming to improve the understanding of the surgeon. With visualization techniques such as fluorescence, 3D modelling and holography, the surgeon is offered a representation of the tumor location, infiltration, depth and surrounding vasculature. Through these techniques the patient-specific pathology is visualized in a potentially more intuitive manner than ioUS. While each technique has advantages and disadvantages, they all aim to improve the patient-specific understanding of the surgeon during intraoperative decision making. This should allow the surgeon to operate more accurately and therewith reduce the number of serious complications.

3Dimensional modelling

The first main component of holographic guided surgery is the development of the 3D model of the patient based on preoperative medical imaging data. 3D models are based on the voxel-by-voxel classification of medical imaging. Each voxel in the image is assigned a specific class which can be the tumor, kidney, artery, background, etc. This is called segmentation, as it divides the image into different segments. Manual, semi-automated or fully automated segmentation algorithms determine this voxel-by-voxel classification. Manual techniques such as thresholding segment the image based on a range of the intensity of the voxel. Semi-automated techniques such as region growing algorithms rely on initial input or “seed” of the user. This seed

propagates through the image as the algorithm determines whether neighboring pixels should be added to the region based on specific limitations set by the user. More automated techniques such as deep learning segmentation algorithms rely on knowledge obtained from training data. General deep learning algorithms, e.g. DeepMedic or UNet, learn on manually segmented data to compute a specific segmentation algorithm during multiple training sessions. After each training session the algorithm becomes more specific for the anatomy it is aiming to segment. The resulting automated algorithms can be very accurate and fast, but they are difficult to implement and require a lot of initial training data.

In the resulting segmentation, each voxel has a dimension resulting in a volume for the individual anatomical models. The combined patient-specific 3D models can be used for preoperative planning as they help improve the spatial understanding of the patient. Wake et al. studied the spatial understanding of urologists based on cross-sectional preoperative imaging (CT or MRI) of 20 adult renal tumor patients (20). They asked three surgeons to pinpoint a digital tumor in the digital kidney based on their patient-specific anatomic understanding from the cross-sectional imaging. The location of the tumor was compared with the actual location in the patient-specific 3D models. Overall, there was a poor overlap of the pinpointed renal tumor and actual tumor (Dice overlap coefficient score of 0.243 ± 0.236). In 16 patients, the pinpointed tumor had no overlap with the actual renal tumor. This demonstrated that understanding spatial relationships based on cross-sectional imaging is a difficult cognitive task, even for experienced surgeons. In earlier work specific for WT surgery in our research group by Wellens et al., it was retrospectively shown that the patient-specific understanding of the pediatric surgeons could be improved with 3D imaging techniques. 3D visualization techniques such as holography and 3D printing were compared with the conventional 2D medical imaging such as CT or MRI for patients with WT (21). However, the described technique was limited by the medical imaging and time-consuming steps such as the segmentation and development of the hologram. The same was concluded by Chaussy et al. in 2020 (25). 3D modelling was considered very useful, but the technique was very time-consuming (mean time of 8.6 hours) and not all imaging was sufficient for this purpose. These are problems which need to be addressed before 3D modelling can be used with holographic surgical navigation.

Apart from preoperative planning, patient-specific 3D models allow for further digital modelling with computer-aided design software (CAD). CAD software can be used to design mechanical models based on the organic anatomical shapes of patient-specific models. This offers

many patient-specific technical applications which can be used before, during and after surgery. Preoperatively, this software can help to design patient-specific simulation phantoms to practice surgery before going to the operation theater (22–24). Intraoperatively, it may be used to design patient-specific implants or surgical navigation guides (25–28). The 3D Lab of the UMC Utrecht has a national leading role in the development of implants. Finally, for the postoperative phase, CAD software is used to design patient-specific cutting guides to position a tumor specimen in a specific direction during slicing by the pathologist (29,30). These examples may indirectly help to improve the surgical outcome of NSS for WT patients in the future.

Holographic positioning

The second key component of holographic guided surgery is the projection of the hologram onto the patient. The hologram needs to be positioned precisely and accurately to be reliable and useful for the surgeon. This requires registration algorithms which correlate intraoperative anatomical landmarks with preoperatively determined digital landmarks based on medical imaging.

After alignment it is crucial to determine the accuracy of the resulting visualization, the alignment error (31). This can be done through measurement of the spatial difference between a visualized holographic landmark and the corresponding landmark with a known position. The difference should be measured in the x, y and z direction to determine the displacement vector. The alignment error can be determined through averaging multiple displacement vectors. In practice, the alignment error can be difficult to determine through observational measurements. Measuring the difference in three directions on an organic object requires accurate calibration of the measurement tool. Moreover, it is challenging to determine the actual center of the holographic landmark. As the hologram is not a real object but only a visual 3D representation, the observer measures a non-existent center point in space. This requires good depth perception, which is a known problem in holographic visualization techniques (32). Finally, a slight shift of the position of the user can cause a shift of the holographic landmark, therewith increasing or decreasing the alignment error. Therefore, the user should remain completely stationary during the measurement. To overcome these difficulties, measurements through more objective techniques are required. Systems such as electromagnetic tracking or robotic calibration might allow for more accurate measurement of the alignment error and are less observer dependent.

With accurate validation studies, we can design a holographic guided surgery system and combine 3D modelling and holographic positioning which is tailored to the surgical need.

1.3 PURPOSES

In this thesis we aim to improve of the possibilities of NSS for WT patients by focusing on clinical and technological developments. Clinically we focus on the harmonization of the preoperative assessment of surgeons. Technically we focus on improvement of the translation of preoperative cross-sectional medical imaging to intraoperative 3D patient-specific anatomy visualization. Lastly, we aim to evaluate NSS through a retrospective study to determine what is still required to further expand the use of NSS for children with renal tumors.

1.4 THESIS OUTLINE

Outline of the chapters for the remainder of this thesis.

Chapter 2

Further expansion of NSS for WT patients requires international harmonization of surgical assessment and technique, to ensure consistent and reliable surgery. This harmonization is essential to improve our efforts in this field. Current guidelines are based on oncological principles. Through surgical consensus we can specify which patients are surgically treatable with NSS and harmonize this assessment worldwide throughout pediatric oncological surgery.

In this chapter we performed a Delphi study. Iteratively developed questionnaires were sent out to an expert panel in the field of NSS for the treatment of WT patients. Through these questionnaires we aimed to develop consensus on which patients are considered feasible for NSS based on concrete surgical criteria.

Chapter 3

In chapter 3 we aimed to overcome technical limitations found in earlier research on 3D visualization technology for children undergoing NSS. In this earlier work of Wellens et al., 3D models were retrospectively used for preoperative planning of WT surgery (21). Limitations arose due to suboptimal cross-sectional medical imaging, long segmentation times and long development times from 3D visualization to 3D model. These limitations restricted the clinical use of 3D models as the development workflow did not fit within the clinical

time frame. Different techniques were introduced and optimized to overcome these limitations for a clinically relevant workflow. These techniques included a novel non-contrast MRI sequence to improve the detail of arterial vasculature, a semi-automated segmentation algorithm to reduce segmentation time, further improvements in holographic software and inhouse 3D printing. After development and optimalization of the workflow, this was tested with a feasibility study in five patients.

Chapter 4

In chapter 4 we introduced a non-contrast MRA sequence for highly accurate arterial vasculature imaging. This sequence is called Non-Contrast Magnetic Resonance Angiography (NC-MRA). The NC-MRA visualizes extra-and intraparenchymal arteries of the kidneys which allows us to develop high-fidelity 3D models. Earlier used conventional MRI sequences were not specific enough. The use of CTA was undesirable due to inherent use of ionizing radiation, that is especially relevant in this young population. This new MRI sequence was introduced as standard of care in every patient with that presented with Wilms' tumor after the finalization of Chapter 3. This sequence was called Non-Contrast Magnetic Resonance Angiography (NC-MRA). The NC-MRA visualizes extra- and intraparenchymal arteries of patients with WT which allows us to develop high-fidelity 3D models. After implementation, the NC-MRA sequence has not been thoroughly tested and validated and thus the question remained on how accurately this sequence works in these young patients in comparison to the conventional imaging.

Therefore, in this chapter, this sequence was retrospectively compared to the conventional MRI sequences by three independent surgeons. They retrospectively scored the imaging at different anatomical levels of all patients to assess the possible added value of the novel NC-MRA sequence for preoperative planning. Moreover, a small prospective assessment was performed.

Chapter 5

After implementation of the new 3D visualization workflow for preoperative planning of WT surgery, 3D models were actively used to determine the surgical plan and communicate within the surgical team. The next step to improve our surgical strategy was the creation of a prediction model based on our operative plan. Further development of our preoperative workflow led to the introduction of virtual resections. This is a tool to digitally perform the planned surgery on the 3D model. This prediction model allows the surgeon to perform measurements on

the digital surgical tumor specimen and derive the remaining volume of kidney parenchyma.

In this chapter we described the use of the Virtual Resection tool on nine retrospective NSS procedures. The aim was to validate the accuracy of the digitally performed surgery through comparison with the actual surgical outcome of the patient. Moreover, we aimed to determine the variation between different observers using the tool and describe the experience of the user using this tool.

Chapter 6

The Virtual Resection tool mimics the upcoming surgery in an exact manner. However, it does not take intraoperative setting into account. In the digital rigid 3D model, it is obvious where the tumor is located and determining the resection depth is straightforward. However, during surgery, it may be more difficult to locate the tumor and determining the resection depth is especially difficult in the actual deformable organ.

To overcome the limitations of our digital workflow, we developed a workflow for phantoms of the involved kidney based on the 3D models of our patients. The surgeons performed mock surgery on these phantoms during a simulated NSS procedure. This simulated intraoperative setting allowed the surgeon to practice the upcoming surgery beforehand. The simulation surgery results were evaluated through MRI to determine the surgical margin of this simulation.

In this chapter we described the workflow by performing simulation surgery for two patients receiving NSS in our center.

Chapter 7

After development of a five-point Procrustes registration algorithm for the HoloLens, a study was needed to determine the accuracy and precision of this technique specifically for patients with renal tumors. The real-world intraoperative situation influences the accuracy of this technique. For example, the deformity of the tissue of the kidney, the difficult localization of anatomical landmarks, the light inside the operating room, the handling of the surgeon and preoperative development time all determine the usability of this technique.

To understand how these variables affect the accuracy, we propose a study in this chapter to measure the accuracy of holographic guided surgery in the operating room during a total nephrectomy. We will perform holographic registration on 20 tumor specimens of patients with a renal tumor. As the tumor and kidney are removed after the holographic positioning, there are no clinical consequences for the

patient. This chapter is a complete overview of this to be performed study which was part of an accepted grant proposal for the Dutch Cancer Society (KWF).

Chapter 8

After implementation of 3D modelling in the clinical workflow, we aimed to evaluate the current surgical outcome of NSS in our center. In this chapter, we performed a retrospective cohort study in patients who have undergone NSS. We evaluated this surgical procedure preoperatively, intraoperatively, and postoperatively. This cohort sets a baseline for further surgical research and technique development. Moreover, it helped to determine what is necessary to further expand the use of NSS for children with renal tumors.

Chapter 9

In the final chapter of this thesis, we discuss the clinical and technological relevance and impact of this work. First, in the technological discussion, we discuss how our developed techniques impact surgical decision making. Furthermore, we assess the added value of these techniques. Secondly, we describe the clinical impact of the Delphi study from Chapter 2 and we describe literature concerning the further implementation of NSS for WT patients. Finally, we give recommendations to further develop and study these techniques, specific for renal tumors patients.

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Chapter 2 Nephron-sparing surgery for patients with Wilms tumors, a surgical Delphi study consensus statement

This chapter is based on

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2.1 ABSTRACT

Background and aim

Within the current SIOP-RTSG treatment protocol, one of the directives for patients with nonsyndromic unilateral Wilms tumor (nsuWT) to be considered for nephron-sparing surgery (NSS) is a tumor volume of less than 300 ml at diagnosis. This volumetric directive does not account for surgical feasibility, possibly reducing the utilization of NSS. To potentially change this directive, a definition of surgical feasibility is required. This study aimed to define surgical consensus statements for the assessment of patients with WT for NSS.

Methods

A Delphi study was performed for which 34 potential experts were approached. Surgeons were included in the expert panel if 3 or more NSS cases per year were performed in their hospital. Among COG surgeons, NSS was not advocated for nsuWT. However, all surgeons were asked to answer the questionnaires without taking their current treatment protocol into account. The first questionnaire contained 5 open-ended questions regarding surgery, oncology, contraindications for NSS, technique, and organization. Follow-up questionnaires contained closed-ended statements based on previous answers.

Results

Nineteen potential experts responded to the first questionnaire. Eleven surgeons were included in the expert panel and continued with three follow-up questionnaires containing 72 statements in total. A median of seven (3 min - 10 max) NSS procedures were performed per year in the hospitals of the experts. Meaningful consensus statements were: 1) bilateral patients should always be considered for NSS regardless of the expected margin. 2) NsuWT patients should receive four weeks of neoadjuvant chemotherapy and have a preoperative tumor volume of <200 ml. 3) Preoperative volume is more important than the volume at diagnosis. 4) Partial nephrectomy with wide resection margin (>5mm) is the preferred technique for nsuWT patients.

Conclusions

Using a Delphi method, surgical experts defined consensus statements regarding NSS for patients with WT. These statements can be used as a starting point to implement surgical feasibility in future treatment protocols and expand the safe utilization of oncologically appropriate NSS.

2.2 INTRODUCTION

Between six to seven percent of all children with a malignancy are diagnosed with a renal tumor (1). Of these patients, around 90% have a Wilms' tumor (WT). In Europe, patients are treated according to the UMBRELLA treatment protocol designed by the International Society for Pediatric Oncology Renal Tumor Study Group (SIOP-RTSG) (2). In this protocol patients receive surgery after neoadjuvant chemotherapy followed by adjuvant chemotherapy and possible radiotherapy. In America, the National Wilms Tumor Study Group of the Children's Oncology Group (NWTSG/COG) recommends primary surgery, followed by chemotherapy and possible radiotherapy. Surgical treatment typically consists of a total nephrectomy (TN) for unilateral disease. Nephron-sparing surgery (NSS) is performed for patients with bilateral disease, patients with genetic (renal) tumor predisposition syndromes or patients with a solitary kidney.

Most patients with nonsyndromic unilateral WT (nsuWT) are treated with a TN combined with (neo)adjuvant chemotherapy showing excellent overall survival over the last decade (2–4). NSS is not commonly performed, and current oncologic guidelines of both SIOP and COG are very strict for this patient group. In the SIOP protocol, patients should have a tumor smaller than 300 ml at diagnosis, an expected substantial amount of functional remaining renal parenchyma, no lymph node involvement and the surgeon should be certain of a negative surgical margin.

The biggest concerns on NSS for unilateral nonsyndromic renal tumors is the increasing oncological risk of NSS (5). This leaves tumor cells behind in the retroperitoneal space and it is typically thought that this increases the risk of a local or regional recurrence. A local recurrence reduces overall survival and thus an increased therapeutic regimen (doxorubicin and/or radiotherapy) is warranted. As a total nephrectomy is standard of care for most cases, the advantages of NSS should significantly outweigh this oncological risk. NSS aims to preserve more functional renal parenchyma which counteracts the long-term disadvantages of TN as a result of the solitary kidney (6). It is known that patients with a remnant solitary kidney after treatment of a pediatric renal tumor have a lower estimated Globular Filtration Rate (eGRF) and a higher blood pressure later in life. It is known that renal functional capacities decrease over time and increase the risk to develop renal injury (7–9). In a larger cohort study of Dutch Childhood Cancer Survivors, a total nephrectomy was a risk factor for a reduced eGFR (8). However, other treatment related factors such as abdominal radiotherapy combined with total nephrectomy, ifosfamide, cisplatin

and carboplatin are risk factors as well. Even the sole fact of having renal tumor treatment increased the odds ratio of decreased eGFR in comparison to a control cohort. Thus, it is difficult to solely attribute a decreased renal function to a total nephrectomy. The whole treatment, including chemotherapy, surgery and radiotherapy, can negatively impact the renal function. Nevertheless, a recent systematic review by Khondker et al. in 2022 of 23 studies looking at the advantages of NSS, suggests NSS for uWT patients may be associated with an improved kidney function and blood pressure in comparison to patients undergoing a total nephrectomy. The current evidence is low, and mean follow-up time was only 9.4 years (range 2.0 – 24.8) for 293 cases of uWT (10). Longer follow-up (40-50 years) will allow for more conclusive answers on this matter, especially considering the decline in eGFR after the fourth decade in life (11).

Currently there are no preoperative surgical feasibility guidelines when a patient with nsuWT may be considered for NSS. Surgical considerations for a patient for this type of surgery are now based on the opinion of the operating surgeon and the current oncological guidelines. This results in issues on definitions, surgical margin assessment and remaining renal parenchyma assessment (12). To further investigate the oncological benefits of NSS, especially for nsuWT patients, there should first be consensus between surgeons for this patient assessment. Earlier estimates of patients with nsuWT eligible for NSS range between five to ten percent (13,14). Ferrer et al. determined based on image-based guidelines that NSS should be feasible in roughly eight percent of the cases enrolled in the COG treatment protocol, not administering neoadjuvant chemotherapy (15). In a post-hoc analysis of pathology specimen for COG, Cost et al. estimate that one in four patients with nsuWT not receiving neoadjuvant chemotherapy have tumor characteristics which are in favor of NSS (16). Whereas, in the SIOP-2001 study performed by the SIOP-RTSG, only three percent of the patients with nsuWT received NSS due to the oncological restraints in the protocol and surgical prudence. Nonetheless, overall survival was good and did not differ between the NSS and TN groups for patients with nsuWT (17).

To overcome the discrepancy between estimated and actual percentages of NSS in patients with uWT, it is first necessary to create clear preoperative surgical feasibility guidelines for the total patient population. This unifies current differences in surgical quality, technique, the use of NSS between centers and facilitates future studies on this debate (18,19). To this end, we have performed a Delphi study regarding the question when it should be surgically feasible to perform NSS in patients with WT. The aim of this Delphi study is to create

consensus-based surgical feasibility statements based on the opinion of expert surgeons. This work aims to harmonize the patient selection for further research.

2.3 METHODS

2.3.1 Study design

The study was initiated by a research team with expertise in the field of pediatric surgery and pediatric urology (MF; AvdS, 15 years of experience; GB, four years of experience; CvdV, 25 years of experience; MW, 25 years of experience; AK, 25 years of experience). The research team determined the initial topics of the first questionnaire. Five different topics relevant for NSS were selected: surgical factors, oncological factors, factors to withhold NSS, technical considerations and organizational factors. Subsequently the research team was divided into three subgroups. The first subgroup (MF, AvdS) developed the questionnaires. The second subgroup (GB, MW) offered feedback and the questionnaire was adapted accordingly by the first subgroup. The first and second subgroup did not participate in the Delphi study. The members of the third subgroup (CvdV, AK) were participants in the study.

The Delphi study started in November 2022 and ended in March 2023 after 4 rounds of questionnaires. The questionnaires were built in Castor EDC and sent to participants by email (20). Each participant was given a pseudonymized research ID which was secured by the research team.

2.3.2 Participant selection

International pediatric surgeons or pediatric urologists were recognized as potential experts in the field of NSS for patients with WT based on recent publications in the field or as known members of the renal tumor study groups of the SIOP-RTSG or NWTSG. During the first round of questionnaires, the potential experts were asked about their experience with the treatment of patients with WT, and specifically their experience with NSS. We decided beforehand to include potential experts to the expert panel if NSS was performed in their hospital equal to or more than three times each year. We aimed to include 10 or more experts in our expert panel. Among COG surgeons, NSS is not advocated for nsuWT. However, the resulting consensus statements were derived from responses across the entire international panel and all surgeons were asked to answer the questionnaires without taking their current treatment protocol into account.

2.3.3 First round of questionnaires

The first round of the Delphi study consisted of two forms. The first form included questions relating to personal information and expertise of the surgeon. Expertise was assessed by asking how many patients with WT are treated in the hospital of the surgeon (both TN and NSS) and how many patients are surgically treated by the surgeon (both TN and NSS).

The second form consisted of five open-ended questions on considerations for NSS. This included surgical, oncological, technical, and organizational factors. We also asked which factors are taken into consideration to withhold NSS from a patient with WT.

2.3.4 Further round of questionnaires

In further rounds of the Delphi study, we divided the questionnaire into five forms, each form directly related to the five open-ended questions from the first round. Each form contained statements which were derived from the answers from the first round. The experts described their level of agreement with statements on a five-point scale by answering: strongly disagree (1), disagree (2), neutral (3), agree (4) or strongly agree (5). At the end of each section, the experts were allowed to elaborate on certain statements in an open text field. At the end of the questionnaire, the experts could report missing subjects for each factor.

In the third round, we introduced each form with a summary of the answers of the statements for which there was consensus in the second questionnaire. Thereafter we reported the statements for which there was no consensus in the second round. We adjusted these statements based on feedback. Moreover, we included statements in this questionnaire if multiple experts reported that this subject was missing in the questionnaire of the second round.

In the fourth round, statements were designed specifically on NSS for patients with nonsyndromic unilateral renal disease as there was a lack of consensus on this topic in the earlier questionnaires. If this again did not result in consensus, we accepted this statement as no consensus.

2.3.5 Data analysis

The responses were prospectively analyzed by the leading subgroup (MF, AdvS). The responses of the first questionnaire were

filtered and clustered in different subjects per factor. These clusters were shared with and controlled by the second subgroup (GB, MW) to ensure quality of the analysis. Together the two subgroups derived multiple statements per topic. For the second, third and fourth round, consensus was defined as an interquartile range (IQR) smaller than or equal to one point on the five-point scale. Consensus was categorized in three categories: agreement (median=>4), neutral (median=3) or disagreement (median=<2). If the IQR was bigger than one, the statement was categorized as no consensus. Cronbach's α was used to determine the reliability of the resulting data from each questionnaire. A Cronbach's α of >0.8 was considered acceptable to continue with a following round.

2.4 RESULTS

2.4.1 Participants

34 surgeons were invited to participate in the Delphi study. Figure 2-1 gives an overview of the number of surgeons responding to each round of the Delphi study. Nineteen (56%) responded to our invitation and questionnaire of round 1. Eight surgeons were not included in the expert panel because they did not meet the inclusion criteria. A total of 11 surgeons were included in the expert panel and received the questionnaire for round 2 (45 questions, α=0.84), which was answered by 10 surgeons. For the following questionnaire (31 questions, α=0.85), 9 experts in the panel responded. Finally, 8 panelists responded to the fourth questionnaire (9 questions, α=0.69). The questions and categorized results given to each statement of the second, third and fourth questionnaire can be found in the supplementary materials. The surgeons in the expert panel treated a median of 7 (3 min and max 10) WT patients in their hospital with NSS each year, of which a median of 5 (1 min and max 10) patients were personally treated by the surgeon each year. Two surgeons from the panel performed total nephrectomy laparoscopically, one surgeon also performed NSS laparoscopically. Results are summarized per form in

Table 2-1.

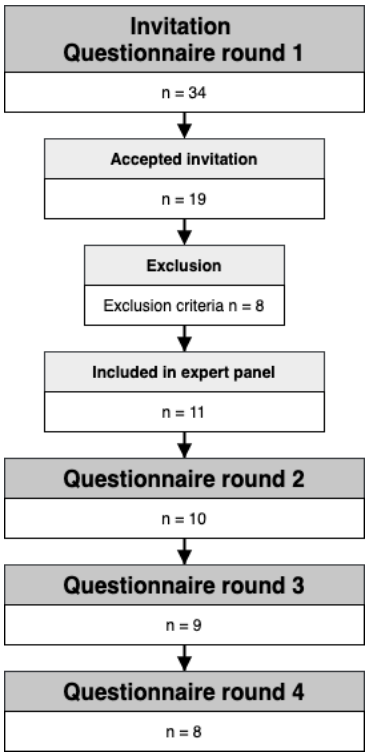

Figure 2-1 Overview of the number of surgeons who completed the questionnaire for each round of the Delphi study.

2.4.2 Surgical considerations

The expert panel agrees that all patients with bilateral disease, a predisposition syndrome, overgrowth syndrome, a solitary kidney, horseshoe kidney or other renal anatomical aberration should be considered for NNS. Patients should receive chemotherapy before performing NSS. The location of the tumor, either exophytic or endophytic, does not matter for the decision to perform NSS. Also, NSS should only be considered if the surgeon expects a clear surgical margin. Patients with cystic non-WT tumors (e.g. CN, CPDN, CWT) should be considered for NSS. Patients with bilateral disease should always be considered for NSS despite of the size or number of tumors before surgery.

2.4.3 Oncological considerations

All stage I / II patients can be considered for NSS. Patients have to be able to adhere to preoperative and follow-up chemotherapy to ensure adequate treatment assessment. If the patient does not respond adequately to preoperative chemotherapy, NSS may still be considered. Oncological principles should not be harmed for the sake of NSS. Patients should preferably be included in a study protocol. Surgeons should always adhere to the current oncological guidelines. Patients who may be considered for NSS should preferably receive 6 to 12 weeks of neo-adjuvant chemotherapy. For bilateral disease, the response to preoperative chemotherapy does not influence the consideration for NSS.

2.4.4 Considerations to withhold NSS

Patients with unilateral disease, metastasis, tumors close to intraparenchymal vessels and polar localizations can all be considered for NSS. Patients with a tumor thrombus in the renal vein / IVC, preoperatively proven anaplasia, and patients without preoperative chemotherapy cannot be considered for NSS. Both unilateral and bilateral patients may be considered for NSS if there is expected lymph node involvement on imaging, provided that the lymph nodes are adequately sampled. Patients with bilateral disease protruding in the urine collection system should be considered for NSS. This is not the case for unilateral patients. If the tumor is close to the intraparenchymal vessels, at least 5 mm away, and if the surgeon is sure of a negative surgical margin, patients with unilateral disease may be considered for NSS. The tumor-intraparenchymal vessel distance should not withhold a bilateral patient from receiving NSS. The amount of extrarenal extension should be taken into account when considering a patient for NSS but should be evaluated per patient.

2.4.5 Technical considerations

Preoperatively, surgical planning requires adequate multidimensional imaging, either CT or MRI. 3D models may be of added value. Intraoperatively, multiple surgical techniques may be considered for NSS including regular partial nephrectomy, enucleation, wedge resection and vertical partial nephrectomy. Laparoscopic or bench surgery should not be used to perform NSS. For unilateral patients, a partial nephrectomy with a wide surgical margin of at least 5 mm is the preferred technique. Bilateral patients should receive NSS on both sides preferably in the same procedure. The kidney and vessels should be

fully mobilized for a safe procedure. There is no preference for the cooling of the renal parenchyma with an ice bath nor for the use of methylene blue or ICG but both techniques may be used for specific cases. Intraoperative ultrasound and surgical loupes with magnification should be used for a safe NSS procedure. Hilar clamping should not be used for all patients, instead hilar control through manual compression may be sufficient. Finally, JJ-stents are not necessary after opening of the urine collection system for a safe NSS procedure. Postoperatively, a DSMA scan may be used to assess the kidney function if there is a clear indication.

2.4.6 Organizational considerations

It is not necessary for a pediatric surgeon to work together with a pediatric urologist during NSS. It is necessary to have a pediatric anesthesiologist with experience with NSS present. All patients undergoing NSS should be sent to an experienced reference center and the pediatric oncologist should feel comfortable with the decision to perform NSS. It can be helpful to have a pediatric radiologist present to assist during intraoperative US. The pediatric ICU department should have a bed available for post operative surveillance for all patients receiving NSS. All patients who may be considered for NSS should be discussed during an interdisciplinary board meeting and supportive renal therapy, such as dialysis, should be available in the performing hospital.

2.4.7 Considerations specific for patients with nsuWT

Patients suspect for nonsyndromic unilateral RTK or CCSK should not be considered for NSS. Patients with nsuWT should at least receive four weeks of neoadjuvant chemotherapy and the tumor should be smaller than 200ml prior to surgery. For these patients, the volume prior to surgery is considered more important than the volume at the moment of diagnosis. Finally, the surgeon may consider a patient with nsuWT if the surgeon expects at least 60% remaining functional renal parenchyma of the affected kidney. The expert panel is neutral on whether the response to neoadjuvant chemotherapy should be taken into account for NSS and this should be evaluated per patient with the multidisciplinary team.

Table 2-1 Summary of the consensus statements resulting from the Delphi study, describing statements for both nonsyndromic unilateral renal tumor patients and bilateral or syndromic unilateral renal tumor patients. NSS: Nephron-sparing surgery.

Form	**Nonsyndromic unilateral renal tumor**	**Bilateral Wilms tumor, syndromic renal tumors or anatomical aberrations**
Surgical considerations	Can be considered for NSS: • unilateral disease, • polar localizations. Tumor should be at least 5 mm away from the intraparenchymal vessels. Turgeon should expect a clear negative surgical margin. Partial nephrectomy is the preferred technique. Should not be considered for NSS: • Unilateral RTK • Unilateral CCSK • WT protruding in the urine collection system.	Must be considered for NSS: • bilateral disease (always), • a predisposition syndrome, • overgrowth syndrome, • a solitary kidney, • horseshoe kidney, • other anatomical aberrations, • metastasis, • WT protruding in the urine collection system. The distance between the tumor and intraparenchymal vessels does not have to be considered. An expected unclear surgical margin is not a reason to withhold NSS. Any surgical technique may be considered, except for a laparoscopic or bench surgery approach. Both sides of a bWT should preferably be operated on in the same procedure.

Form	Nonsyndromic unilateral renal tumor	Bilateral Wilms tumor, syndromic renal tumors or anatomical aberrations
Oncological considerations	Should receive at least 4 weeks of neoadjuvant chemotherapy. Tumor should have a preoperative volume of <200 ml. Surgeon should expect >60% remaining healthy renal parenchyma.	Should preferably receive at 6 to 12 weeks of neoadjuvant chemotherapy. Response to preoperative chemotherapy does not influence considerations.
Considerations to withhold NSS	Patients should not be considered for NSS if: • tumor thrombus in the renal vein / IVC, • preoperatively proven anaplasia, • without preoperative chemotherapy The amount of extrarenal extension should evaluated per patient.	All patients with bilateral disease should be considered for NSS.
Technical considerations	NSS should be performed by the partial nephrectomy technique. The following surgical techniques should be used: • Intraoperative ultrasound, • surgical loupes with magnification • adequate preoperative imaging The following techniques may be used: • 3D modelling	NSS can be performed by the following techniques: • enucleation, • wedge resection • regular or vertical partial nephrectomy The following techniques should be used: • Intraoperative ultrasound, • surgical loupes with magnification • adequate preoperative imaging

Form	Nonsyndromic unilateral renal tumor	Bilateral Wilms tumor, syndromic renal tumors or anatomical aberrations
	• Hilar control through manual compression	The following techniques may be used: • cooling with an ice bath • methylene blue or ICG • 3D modelling • Hilar control through manual compression • Clamping of the vessels
Organizational considerations	The following prerequisites should be met for NSS: • a pediatric anesthesiologist with experience with NSS, • taking place in an experienced reference center, • Pediatric oncologist should feel comfortable with the decision, • Bed available at the pediatric ICU, • Supportive renal therapy available, • Patient should have been discussed during an interdisciplinary board meeting.	The following prerequisites should be met for NSS: • a pediatric anesthesiologist with experience with NSS, • taking place in an experienced reference center, • Pediatric oncologist should feel comfortable with the decision, • Bed available at the pediatric ICU, • Supportive renal therapy available, • Patient should have been discussed during an interdisciplinary board meeting.

2.5 DISCUSSION

With this study, we have defined consensus on the surgical feasibility assessment by consulting an international group of experts through a Delphi methodology. Current oncologic treatment protocols do not contain standardized surgical feasibility guidelines for the assessment of nephron-sparing surgery for patients with Wilms' tumors. The oncological protocols extensively describe chemotherapeutic treatment regimens for each different risk group based on diagnosis and histology. However, surgical treatment considerations are not specifically described. Moreover, the patient assessment prior to surgery is not well described, yet this is assessment crucial for surgical decision making. Therefore, these surgical consensus statements should be considered complementary to the current ruling oncological guidelines and allow further development of surgical guidelines.

The most important oncological risk of NSS is the possibly incomplete resection or positive surgical margin. However, the influence of a positive surgical margin and a local recurrence is not that explicit. In 2013, Kieran et al. retrospectively assessed all bWT patients undergoing NSS in their center, including 21 patients. Out of five patients with a positive surgical margin (24%), only one patient had a local recurrence after treatment with adjuvant flank radiotherapy. The authors conclude that bWT patients with a microscopic positive margin are not at a higher risk for local recurrence. (21) The same was observed in the SIOP-2001 study. Out of 91 uWT patients treated with NSS, eight patients (9%) had a positive surgical margin treated with adequate postoperative therapy out of which one patient had a local recurrence (22). Groenendijk et al. 2021 concluded that NSS does not appear to be a prognostic factor for local recurrence, if performed by experienced surgeons and patients are carefully selected (23).

The essential underlying rationale for this low number of local recurrences after a positive surgical margin is the postoperative abdominal radiotherapy for all except low risk patients (24). Subsequently, this also raises the question of the influence of radiotherapy on the surgically treated remaining renal parenchyma if a surgical positive margin were to occur. Radiotherapy supposedly counteracts the positive functional benefit of NSS, which is a considerable argument against the use of NSS for nsuWT (25). As mentioned earlier, abdominal radiotherapy in combination with a total nephrectomy is a risk factor for a decreased eGFR in childhood cancer survivors (8). However, this is likely very related to the given radiotherapy dosage and of course the total nephrectomy. The Pediatric Normawl Tissue Effects in the Clinic (PENTEC) task force recently

described the risk of renal toxicity after radiotherapy on the total kidney volume (26). Based on their review, they conclude that the risk of chronic or severe toxicity to the kidney is low (<5%) if the cumulative dose on the total volume of the kidney remains under 11 Gy in 7 fractions. This dosage is the standard of care for patients with a positive surgical margin. This risk of renal toxicity increases if nephrotoxic chemotherapeutics are given (Carboplatin, Cisplatin or Ifosfamide), but these are not regularly prescribed to nonsyndromic unilateral patients. Thus, the decrease in renal function of the spared kidney is limited. Patients may only suffer from a mildly decreased GFR of this affected kidney, with a normally functioning kidney on the contralateral side. Looking specifically at kidney function, radiotherapy seems not to counteract the positive effect of NSS for usWT patients. However, it is necessary to mention that despite a low burden of <11 Gy of radiotherapy on remaining renal parenchyma, a positive surgical margin and therewith radiotherapy should always be avoided due to the inherent risk of secondary malignancies, other radionecrosis related complications and significantly increased therapeutic burden for the patient (8,27,28). To mitigate the risk of upstaging and radiotherapy, NSS should only be considered in properly specific selected cases in line with the consensus statements.

It is important to recognize that, despite of the consensus reached, there were different rationales within the international panel, especially on the topic of NSS for nsuWT patients. These differences in rationale originated from the significant differences in oncological guidelines between the SIOP-RTSG and COG treatment protocols and have recently been well described (29). For example, for nsuWT patients, SIOP includes preoperative chemotherapy which aims to create a tumor capsule and reduce tumor volume, possibly allowing for NSS. Under COG, (ns)uWT patients do not receive preoperative chemotherapy and directly undergo a total nephrectomy. Therefore, surgeons within the COG treatment protocol do not advocate NSS for nsuWT patients. This evidently contradicts the surgical feasibility consensus statements for these nsuWT patients. However, we deliberately chose to include experts from both treatment protocols. All surgeons were asked to answer the questionnaires without taking their current treatment protocol into account. Therefore, the derived consensus statements should be seen as treatment protocol independent. As such, we may be able to implement these consensus statements on surgical feasibility in both future treatment protocols and still allow for oncologically appropriate utilization of NSS.

To facilitate this adaptation of protocols, first the potential impact for patients with WT needs to be quantified. This may be studied

by assessing imaging of patients with the proposed guidelines in a large retrospective cohort. This should result in an observer-independent percentage of patients with either bilateral or unilateral WT eligible for NSS. Moreover, these results should be compared to earlier cohort studies. Current SIOP-RTSG Umbrella guidelines advocate that NSS may be indicated for patients with nsuWT if they have a diagnostic tumor volume <300ml, as patients with a diagnostic tumor volume >318 ml have a higher chance of lymph node metastasis, though the overall rate of positive lymph nodes is small (5.5%) (25). No specific preoperative volume was reported for a significant difference in lymph node status, possibly due to the overlapping ranges in preoperative volume between a positive and negative lymph node status making it a difficult to classify (median LN- 130 (IQR 44-294); median LN+ 192 (IQR 63-548); ml). However, in our Delphi study, the panel agreed that the preoperative volume is surgically more important than the diagnostic volume to consider a nsuWT patient for NSS. The surgeons consider NSS feasible for nsuWT patients if the tumor has a preoperative volume <200 ml. More retrospective analyses are necessary to determine a preoperative volume which relates oncologic safety with surgical feasibility. Regardless of the surgical technique used, adequate lymph node sampling should always be performed.

2.5.1 Limitations

This study followed the conventional Delphi methodology in which participants largely contributed to the contents of the questionnaires (30). As our expert panel was small due to strict inclusion criteria, the contents only describe the opinion of a select group of surgeons. However, NSS for WT patients is a treatment option only performed by a very small number of surgeons worldwide. Therefore, these strict inclusion criteria ensured only experienced surgeons in this field were included. This increases the value of these consensus statements. Moreover, we ensured surgeons from both large international treatment protocols were included. Thus, we do not believe that a potentially bias was introduced by the small expert panel.

There is no discrimination between evidence-, experience-, or opinion-based consensus statements as we only aimed to derive the overall opinion of the expert panel. This devaluates the results of a Delphi study, lowering the level of evidence, which is a known disadvantage of this technique. Thus, this study should be seen as a harmonization of the general expert knowledge.

2.6 CONCLUSION

Using a Delphi study, a panel of surgical experts defined consensus statements regarding the appropriate use of NSS for patients with WT. These statements can be used to implement surgical feasibility in treatment protocols and expand the utilization of safe and oncologically appropriate NSS.

2.7 REFERENCES

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2.8 SUPPLEMENTARY MATERIALS

Supplementary table 2 - 1: Overview of the questions and answers given for the second round of the Delphi study When to perform NSS for WT patients. Consensus was defined as an IQR equal to or smaller than one. If there was consensus, the statement was categorized in agreement (median => 4), neutral (median = 3) or disagreement (median =< 2).

Question	Median	Min	Max	IQR	State
Surgery					
Patients with bilateral disease, a solitary kidney, a horseshoe kidney, or other anatomical aberration should be considered for NSS.	5	4	5	0	Agreement
Patients with a predisposition or overgrowth syndrome should be considered for NSS.	5	4	5	1	Agreement
Patients with an expected non-WT should be considered for NSS.	3	1	4	2	No Consensus
Patients who can be considered for NSS should receive preoperative chemotherapy.	5	1	5	1	Agreement
Patients with a small tumor volume before surgery should be considered for NSS.	4	3	5	1	Agreement
NSS should only be considered for patients with an exophytic tumor.	2	1	5	0	Disagreement
NSS should only be considered if the surgeon expects a large amount of functional remaining renal	3	1	4	2	No Consensus

Question	Median	Min	Max	IQR	State
parenchyma after tumor removal.					
NSS should only be considered if the surgeon expects a complete surgical margin.	4	1	5	1	Agreement
Oncology					
Stage I / II patients should be considered for NSS.	4	2	5	0	Agreement
Patient should be able to adhere to the postoperative chemotherapy regimen before considering NSS.	4	3	5	0	Agreement
Patients should be included in a study protocol before considering NSS.	4	1	5	2	No Consensus
Patients can only be considered for NSS if they have an adequate response to preoperative chemotherapy.	2	1	4	1	Disagreement
There are no purely oncological factors to take into account when considering a patient for NSS.	2	1	5	0	Disagreement
Withhold					
Unilateral WT patients can be considered for NSS.	4	2	5	0	Agreement
Patients with metastasis can be considered for NSS.	4	3	5	1	Agreement
Patients with lymph node involvement can be considered for NSS.	4	1	5	2	No Consensus
Patients younger than 6 months can be considered for NSS.	4	2	5	0	Agreement

Question	Median	Min	Max	IQR	State
If the tumor infiltrates in the urine collection system, the patient can be considered for NSS.	4	1	5	2	No Consensus
Patients with a tumor in close proximity to intraparenchymal vessels can be considered for NSS.	4	3	5	0	Agreement
Patients with a tumor thrombus in the renal vein / IVC can be considered for NSS.	2	2	5	1	Disagreement
Patients with preoperatively proven anaplasia can be considered for NSS.	1	1	3	1	Disagreement
Patients with a polar localization can be considered for NSS.	4	4	5	0	Agreement
Patients without preoperative chemotherapy can be considered for NSS.	2	2	4	1	Disagreement
Technology					
Partial nephrectomy with wide surgical margin can be the preferred surgical technique to safely perform NSS.	3	2	5	2	No Consensus
Enucleation can be the preferred surgical technique to safely perform NSS.	4	2	4	1	Agreement
Obtaining a narrow surgical margin can be the preferred surgical technique to safely perform NSS.	3	2	4	2	No Consensus
Wedge resection can be the preferred surgical technique to safely perform NSS.	4	2	4	1	Agreement

Question	Median	Min	Max	IQR	State
Vertical partial nephrectomy can be the preferred surgical technique to safely perform NSS.	4	2	5	1	Agreement
Bench surgery can be the preferred surgical technique to safely perform NSS.	2	1	4	1	Disagreement
Laparoscopic partial nephrectomy can be the preferred surgical technique to safely perform NSS.	2	1	3	1	Disagreement
Kidney and vessels should be completely mobilized to safely perform NSS.	4	1	5	1	Agreement
Intraoperative US should be used to safely perform NSS.	4	3	5	1	Agreement
Ice bath for cooling of the kidney should be used to safely perform NSS.	3	2	4	1	Neutral
Surgical loupes with magnification should be used to safely perform NSS.	4	3	5	1	Agreement
Methylene blue or ICG should be used to safely perform NSS.	3	1	4	0	Neutral
Preoperative planning with CTA should be used to safely perform NSS.	4	2	5	1	Agreement
Preoperative planning with 3D models should be used to safely perform NSS.	3	2	5	2	No Consensus
After opening of the Urine Collection System, double J-stents should be used to safely perform NSS.	2	1	3	1	Disagreement
Renography should be used to assess the kidney function after NSS.	2	1	5	2	No Consensus

Question	Median	Min	Max	IQR	State
Organization					
A pediatric surgeon and a pediatric urologist should perform NSS together.	2	1	5	1	Disagreement
An experienced pediatric anesthesiologist should be present when performing NSS.	5	2	5	1	Agreement
A pediatric radiologist should be available for intraoperative US when performing NSS.	4	2	5	3	No Consensus
The pediatric oncologist should feel comfortable with NSS for his or her patient.	4	3	5	0	Agreement
A bed should be available at the pediatric ICU department for post OP surveillance.	4	2	5	2	No Consensus
A patient should be sent to an experienced reference center for NSS.	5	4	5	0	Agreement

Supplementary table 2- 2: Overview of the questions and answers given for the third round of the Delphi study When to perform NSS for WT patients. Consensus was defined as an IQR equal to or smaller than one. If there was consensus, the statement was categorized in agreement (median => 4), neutral (median = 3) or disagreement (median =< 2).

Question	Median	Min	Max	IQR	State
Surgery					
Patients with cystic non-WT tumors (e.g. CN, CPDN, CWT) should be considered for NSS.	4	2	5	0	Agreement
Patients with aggressive non-WT tumors (e.g. RTK, RCC,	3	1	4	2	No Consensus

Question	Median	Min	Max	IQR	State
CCSK, CMN) should be considered for NSS					
Patients with unilateral disease with a tumor smaller than 200 ml or 50% of the kidney volume before surgery should be considered for NSS	4	2	5	2	No Consensus
Patients with bilateral disease should always be considered for NSS regardless of the size or amount of tumors before surgery	5	1	5	0	Agreement
Patients with unilateral disease may be considered for NSS if the surgeon expects more than 50% of remaining functional renal parenchyma.	4	2	5	2	No Consensus
Patients with bilateral disease should always be considered for NSS despite of the expected amount of functional renal parenchyma.	4	2	5	3	No Consensus
Oncology					
Patients should preferably be included in a study protocol before considering NSS	4	3	5	1	Agreement
Patients with unilateral disease may be considered for NSS if the patient shows an adequate response to chemotherapy, either in radiological volume or ADC values.	4	2	5	3	No Consensus
Patients with bilateral disease should always be	5	3	5	1	Agreement

Question	Median	Min	Max	IQR	State
considered for NSS despite the response to chemotherapy					
Patients who may be considered for NSS should receive 6 to 12 weeks of neo-adjuvant chemotherapy	4	2	5	1	Agreement
Surgeons should always adhere to oncological principles when considering a patient for NSS.	5	1	5	0	Agreement
Withhold					
Patients with unilateral disease with expected lymph node involvement on imaging may be considered for NSS.	4	2	5	1	Agreement
Patients with bilateral disease with expected lymph node involvement on imaging may be considered for NSS.	5	2	5	1	Agreement
Patients with unilateral disease with tumor infiltration in the urine collection system may be considered for NSS.	2	1	4	1	Disagreement
Patients with bilateral disease with tumor infiltration in the urine collection system may be considered for NSS.	4	2	5	1	Agreement
Patients with unilateral disease may be considered for NSS if the tumor is at least 5 mm away from intraparenchymal vessels to ensure a safe margin.	3	2	5	1	Neutral

Question	Median	Min	Max	IQR	State
Patients with unilateral disease may be considered for NSS if the tumor is at least 1 cm away from intraparenchymal vessels to ensure a safe margin.	3	2	5	1	Neutral
Patients with bilateral disease may be considered for NSS if the tumor is touching intraparenchymal vessels.	4	3	5	0	Agreement
Patients with extrarenal extension may be considered for NSS.	3	2	5	1	Neutral
Patients with unilateral disease with expected lymph node involvement on imaging may be considered for NSS.	4	2	5	1	Agreement
Technology					
For unilateral patients, partial nephrectomy with wide (more than 5 mm) surgical margin is the preferred surgical technique to safely perform NSS.	4	2	5	1	Agreement
For bilateral patients, partial nephrectomy is the preferred surgical technique to safely perform NSS regardless of the expected size of the margin.	4	1	5	3	No Consensus
Preoperative planning with 3D models can be of added value to safely perform NSS	5	3	5	1	Agreement
Renography can be used to assess the kidney function	4	3	5	0	Agreement

Question	Median	Min	Max	IQR	State
after NSS if there is a clear indication to do so.					
Hilar clamping should be used to safely perform NSS.	2	1	3	1	Disagreement
Patients with bilateral disease preferably undergo NSS on both sides in the same procedure.	4	2	5	1	Agreement
For unilateral patients, partial nephrectomy with wide (more than 5 mm) surgical margin is the preferred surgical technique to safely perform NSS.	4	2	5	1	Agreement
Organization					
The presence of a pediatric Radiologist can be helpful during intraoperative US when performing NSS.	4	2	5	1	Agreement
A bed should be available at the pediatric ICU department for post OP surveillance of all NSS cases	4	1	5	1	Agreement
A bed should be available at the pediatric ICU department only for post OP surveillance of difficult cases	5	1	5	0	Agreement
Patients who may be considered for NSS should always be discussed during interdisciplinary board meeting.	5	2	5	0	Agreement
Supportive renal therapy such as dialysis should be present in the hospital when performing NSS.	5	4	5	0	Agreement

Supplementary table 2 - 3: Overview of the questions and answers given for the third round of the Delphi study When to perform NSS for WT patients. Consensus was defined as an IQR equal to or smaller than one. If there was consensus, the statement was categorized in agreement (median => 4), neutral (median = 3) or disagreement (median =< 2).

Question	Median	Min	Max	IQR	State
nsuWT					
Patients with a suspected RTK may be considered for NSS.	2	1	4	0.5	Disagreement
Patients with a suspected RCC may be considered for NSS.	3	1	5	2.25	No Consensus
Patients with a suspected CCSK may be considered for NSS	2	1	3	0.25	Disagreement
Patients with a suspected CMN may be considered for NSS.	3.5	1	5	1.25	No Consensus
Patients with nonsyndromic unilateral disease may be considered for NSS if the tumor is smaller than 200 ml prior to surgery.	4	3	5	0.25	Agreement
The volume of the tumor at the moment of surgery is more important than the volume at the moment of diagnosis for the consideration of NSS.	5	4	5	1	Agreement
Patients with nonsyndromic unilateral disease may be considered for NSS if the surgeon expects at least 60% remaining functional renal parenchyma of the affected kidney.	4	2	5	0.5	Agreement
Patients with nonsyndromic unilateral disease may be considered for NSS regardless of the response to neoadjuvant chemotherapy.	3	2	5	0.5	Neutral

Question	Median	Min	Max	IQR	State
Patients with nonsyndromic unilateral disease may be considered for NSS after receiving four weeks of neoadjuvant chemotherapy if the tumor is easily resectable.	4	3	5	1	Agreement

Chapter 3 MRI Based 3-Dimensional Visualization Workflow for the Preoperative Planning of Nephron-Sparing Surgery in Wilms' Tumor Surgery: a Pilot Study

This chapter is based on

Fitski, M., Meulstee, J. W., Littooij, A. S., van de Ven, C. P., van der Steeg, A. F., & Wijnen, M. H. *(2020)* MRI Based 3-D imensional Visualization Workflow for the Preoperative Planning of Nephron-Sparing Surgery in Wilms' Tumor Surgery: A Pilot Study. *Journal of Healthcare Engineering.*

3.1 ABSTRACT

Purpose

Due to the size and localization of Wilms' tumor (WT), nephron-sparing surgery (NSS) is only possible in a limited number of cases. When NSS is considered, the surgeon preoperatively requires a thorough understanding of the patient-specific anatomy to prevent positive surgical margins and other complications. Through a collaboration between the radiology and pediatric surgery departments and 3D imaging specialists, a 3D visualization workflow was developed to improve preoperative planning of NSS for WT patients.

Methods

The 3D visualization workflow combines a MRA sequence, a segmentation protocol and Augmented Reality (AR) visualization, additional to in-house 3D printing. A non-contrast enhanced MRA scan was added to the MRI protocol. MRI sequences were segmented with a segmentation protocol in an open-source software package. The resulting 3D models were visualized in AR with a HoloLens and 3D printed.

Results

In a pilot study, five WT patients eligible for NSS were preoperatively planned through the 3D visualization workflow. The AR visualization software was fast, free to use and allowed adequate handling of the 3D holograms. The 3D printed models were considered convenient and practical for intraoperative orientation. The patient-friendly, fast and low-cost 3D visualization workflow was easily implemented and appeared to be valuable for the preparation of NSS.

Conclusion

This pilot study demonstrates how a strong collaboration between the pediatric surgery and radiology departments and 3D imaging specialists will help to shape the future of pediatric oncological surgery. This 3D visualization workflow aims to prepare pediatric oncological surgeons prepare for nephron-sparing surgery in patients with Wilms' tumors.

3.2 INTRODUCTION

Wilms' tumor (WT) is the second most common abdominal pediatric tumor in Europe, with children being diagnosed at a median age of approximately 3.5 years (1). In accordance with the International Society for Pediatric Oncology – Renal Tumor Study Group (SIOP-RTSG) Umbrella treatment protocol, therapy generally consists of neoadjuvant chemotherapy, followed by radical nephrectomy and adjuvant chemotherapy (2). In contrast to a radical nephrectomy for local treatment, nephron-sparing surgery (NSS) can be used for nephrogenic preservation. This helps to protect the patient from excessive functional parenchymal loss in the future (3). NSS is a technically demanding procedure and it requires a thorough preoperative understanding of the patient-specific renal anatomy and intra-parenchymal vasculature (4). Patients with bilateral disease, with or without a predisposing syndrome, might be eligible for NSS depending on the tumor location, size, and infiltration. Due to the risk of a positive surgical margin with NSS, unilateral non-syndromic patients are treated with a radical nephrectomy. However, in order to prevent late effects of a radical nephrectomy at a young age, these patients might be still considered for NSS if they have a small lesion at a favorable location at the moment of diagnosis (2). Therefore, careful selection and preoperative planning is crucial to ensure a positive oncological outcome in combination with low morbidity.

For the preoperative planning of NSS, patient-specific 3-dimensional (3D) anatomical models are increasingly used (5–7). This is due to the improved and more accessible imaging, segmentation, and visualization techniques. 3D printing is a visualization technique which can be used to visualize these patient-specific models. The positive effects of 3D printed anatomical models in adults have been described and include reducing blood loss, reducing intraoperative complications, and improving patient education (5). In renal surgery for pediatric oncology, 3D printed anatomical models are not frequently used and if so, only on a case-by-case basis (3,8–11). Regarding NSS, 3D printed models are mainly useful for assisting in planning the vascular dissection. However, the vasculature information in current 3D models remains poor, primarily due to low image quality (8). Retrospectively, personalized 3D anatomical models have shown a significant improvement of the anatomical understanding for the renal artery, vein, tumor, and urinary collecting system and may potentially help pediatric surgeons prepare for NSS (12). The models were limited, due to low image quality and modelling techniques which are labor intensive, require a long processing time and are expensive.

High quality imaging is crucial for high-fidelity anatomical models, as the imaging quality primarily determines the model quality. Preoperative magnetic resonance imaging (MRI) is already a vital part of the SIOP-RTSG Umbrella treatment protocol and can be used for 3D visualization, as Wake et al. (2017) have previously shown for renal cancer in adults (13). An additional computed tomography angiography (CTA) scan can be performed for high quality arterial imaging, yet it is undesirable due to the radiation and contrast administration. Moreover, an additional CTA scan prolongs the preoperative workup which is already considered highly stressful for pediatric patients. Therefore, techniques solely based on the preoperative MRI are favorable. Wake et al. (2017) reported challenges in standardized high-resolution imaging and were also limited by the manual segmentation procedure. Image processing took around 7 hours and 3D printing costs were around $1000 (US dollar) per model. To overcome these limitations, our aim is to develop a 3D visualization workflow in which imaging, segmentation, and visualization techniques are combined, to suit the specific preoperative requirements needed for planning NSS of WT in pediatric patients.

3.3 MATERIALS AND METHODS

In close collaboration with the departments of radiology and pediatric surgery, 3D imaging specialists have designed a new 3D visualization workflow for the preoperative planning of NSS in WT patients. In this workflow, we addressed the limitations in usability and model quality previously described in literature. An overview of the proposed workflow is given in Figure 3-1. The following subsections describe the employment of the non-contrast enhanced MRA (NC-MRA) sequence, segmentation protocol and visualization with Augmented Reality (AR) and with 3D printing.

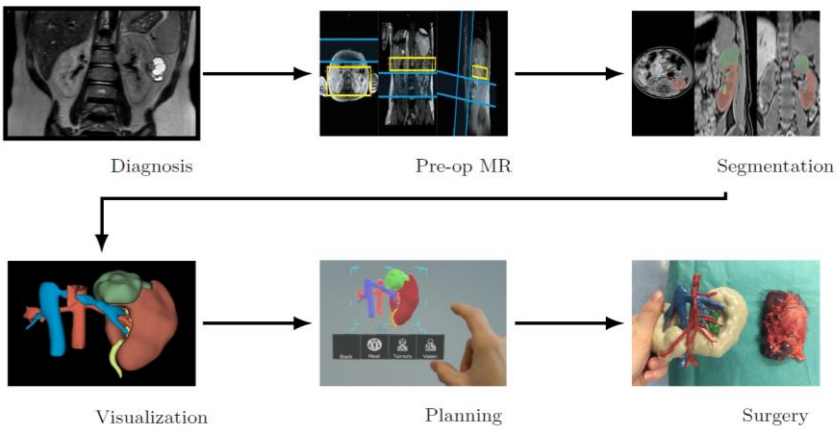

Figure 3-1 Schematic overview of proposed preoperative 3D visualization workflow. After diagnosis and neoadjuvant chemotherapy, a WT patient receives a preoperative MRI. A high-resolution non-contrast enhanced MRA sequence is added to the protocol to allow for visualization of the intraparenchymal arteries. The MRI scans are segmented through a standardized segmentation protocol in 3DSlicer resulting in patient specific 3D anatomical models. The 3D models are displayed for preoperative planning in Augmented Reality through a HoloLens. 3D printed models can be brought inside the operating theatre.

3.3.1 Imaging

The standard pediatric kidney tumor MRI protocol was performed at presentation and after the neoadjuvant chemotherapy in accordance with the SIOP-RTSG Umbrella protocol. A 1.5 Tesla system (Achieva; Philips Medical Systems, Best, Netherlands) was used for all patients. The imaging protocol consisted of coronal 3D T2-weighted (-W) sequence, fat-suppressed T1-W sequence, diffusion-weighted imaging (b values of at least 0, 100 and 800 s/mm^2) and a fat-suppressed T2-W sequence. Before administering contrast agent, the NC-MRA sequence was acquired. During the administration of intravenous contrast (Gadovist; Bayer Pharma, Berlin, Germany at a dose of 0.1 mmol / kg body weight) a 4D contrast enhanced MRA was acquired after which a post-contrast fat suppressed T1-W sequence was performed. Children were awake, sedated or under anesthesia depending on their ability to cooperate. Hyoscine butylbromide (Buscopan, Boehringer Ingelheim Limited, Bracknell, UK) was administered at an intravenous dose of 0.4 mg/kg body weight to reduce the peristaltic artefacts.

The used NC-MRA is an inflow-enhanced balanced Steady State Free Precession (b-SSFP) sequence. This sequence has a unique T2/T1 contrast, which has a high contrast for blood. The sequence is scanned with a high reconstructed resolution (0.56, 0.56, 1 mm), takes 3 - 5 minutes to scan, is independent of direction and does not require a contrast agent. An inversion time (TI) of 450 ms was used. If 450 ms was not possible due to a fast heart rate, the TI was lowered based on the maximal allowed TI (90 % of the R-R interval). The cardiac trigger was set on a heartbeat measured preferably with a three-lead electrocardiogram or else with a physiological pulse unit. The transverse field of view (FOV) was set parallel to the renal artery of the affected kidney in the coronal view using the 3D T2-W sequence. The FOV encompasses the complete intra-parenchymal arterial branch. A saturation band was positioned below the lower pole of the kidneys and a fat saturation band was positioned at the ventral aspect of the abdomen. This allowed saturation of signal from the vena cava and abdominal fat.

3.3.2 Segmentation

A selection of the MRI sequences (3D T2-W, NC-MRA, post-contrast fat-suppressed T1-W) was used to perform the segmentation in the open-source software package 3DSlicer 4.10.2 A standardized protocol was developed for the segmentation of the arteries, veins, urine collecting system (UCS), tumor and kidney. Firstly, the NC-MRA sequence was used to compute the segmentation of the arteries through an intensity-based threshold technique. The "scissor"-tool was used to remove artefacts and the resulting model was smoothed with a Gaussian filter. The arterial segmentation was used as an overlay in the T2-W sequence in order to differentiate intra-parenchymal arteries and veins. Subsequently, the veins and UCS were segmented with an intensity-based brush in the aforementioned sequence. The post-contrast fat-suppressed T1-W sequence was used for the segmentation of the tumor and kidney with a Grow-Cut algorithm (14). This algorithm uses labels in the area of the tumor, kidney and background in several slices in order to compute the border between the three labels. The results were filtered with a joint-smoothing filter. Any under- or oversegmentations were manually corrected. The resulting segmentations were exported as a stereolithography (.STL) file.

3.3.3 Visualization

In order to visualize the 3D models in .STL format and the T2-W images (DICOM format) were added to the AR software developed in

Unity 5.5.2 (Unity Technologies; San Francisco, CA, USA). The AR software ensured that the 3D models and MRI images were spatially aligned. Subsequently, the AR software computed a patient-specific container which could be uploaded to a visualization library installed on the head-mounted display.

Preoperatively, the surgeon reviewed the patient-specific AR hologram in a real-world setting to prepare for surgery. The surgeon had full control over the hologram: the surgeon could translate, rotate and scale the hologram. Additionally, the transparency of the individual anatomical models could be adjusted, and the individual models could be removed. It was possible to look at the T2-W MRI in three different planes (transverse, sagittal and coronal) in order to correlate the orientation of the 3D models with the more commonly known MRI images. The AR-display from the HoloLens could be shared on a PC through a livestream to allow for an interactive discussion by the user and observers. This visualization technique has been free of costs after development of the software and purchasing the HoloLens.

To create physical anatomical models, an Ultimaker S5 dual-extrusion printer was used with a Fused Filament Fabrication technique. To allow visualization of the renal pelvis, the 3D modelled kidney could be bisected in Meshmixer 3.5.474 (Autodesk, Inc., San Francisco, CA, USA) with a plane cut prior to printing. The resulting models were printed with a fine layer profile of 0.1 mm thick, infill density of 30 % (zigzag infill pattern) and support overhang angle of 60°. The models were printed with two different colors which allowed us to improve the contrast of specific anatomical regions. 3D printed models allowed the surgeons to get a sense of the tumor size and the model could be taken into the OR by an assistant to help the surgeon navigate during the procedure.

3.4 RESULTS

Between May 2019 and August 2019, a pilot study was performed. Five patients were considered for NSS and their surgeries were preoperatively planned with the 3D visualization workflow in addition to the standard protocol. The patients' ages ranged from 2 to 8 years old (mean 5.2 ± 1.4 years). Patient demographics, tumor characteristics and relevant technical outcomes for each patient are described in

Table 3-1.

The mean additional scanning time required for the NC-MRA sequence was 04:12 ± 00:36 minutes. The mean segmentation time was 41 ± 19 minutes, which seemed closely correlated to the number and size of the lesions. The mean volume of the resulting tumor 3D model was 12.2 ± 20.5 ml per lesion. Average 3D printing time was roughly 20 hours. Manual removal of supporting structures during the post-processing took about half an hour.

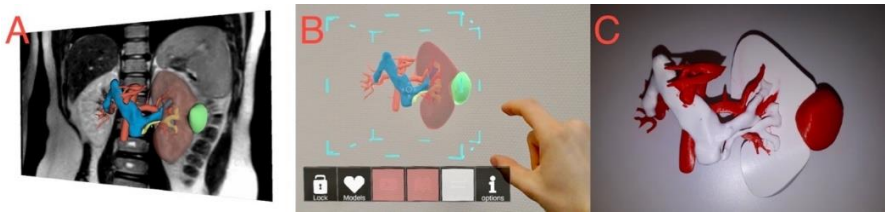

Figure 3-2 Three different visualization techniques for the MRI-based 3D models of patient 3. The patient has a transposition of the inferior vena cava below the superior mesenteric artery. A = 2D screenshot of 3D rendering in 3DSlicer with a coronal T2-weighted MRI slice; B = Augmented Reality through the head-mounted display (HoloLens), holding the blue "cube" allows for translation of the hologram; C = 3D printed model printed with polylactid acid in an Ultimaker S5, the kidney is bisected.

The MRA sequence added to the preoperative MRI was successful in all patients. The segmentation and visualization in AR were performed within a day after the preoperative MRI. Figure 3-2 shows a 2D rendering in 3DSlicer, a 3D hologram visualized with the head-mounted display, and a 3D print of a 3D anatomical model all of the same patient. The 3D printers generally printed the models overnight allowing ample time for the surgical team to assess the 3D models. The arterial models visualized the intra-parenchymal arteries up to the second or third segmental arterial branch. The level of detail of the vein and UCS 3D models were noticeably less than the level of detail of the arterial models. However, surgeons considered the vein and UCS 3D models supportive and additional to the MRI imaging.

The AR visualization allowed the surgeons to assess the depth of resection with regard to renal arteries, veins, and UCS. Being able to scale, move, rotate, and walk around the hologram was very useful for the understanding of the patient-specific anatomy. Intraoperatively, an assistant showed the 3D printed models to visualize the location and

rotation of the tumor in relation to the renal parenchyma. This proved to be mainly useful in the patients with multiple lesions.

Table 3-1. Preoperative patient demographics, tumor characteristics and pathologic outcomes for each patient together with the non-contrast enhanced MRA (NC-MRA) scanning duration, the duration of the complete segmentation, the tumor volume derived through 3DSlicer and 3D printing time and costs. NSS = nephron-sparing surgery

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Gender (M/F)	F	F	M	F	F
Age (Y)	8	2	4	5	3
Disease	Unifocal right	Unifocal right, bilateral nephro-blastomatosis	Unifocal left	Bilateral, multifocal	Bilateral, nephro-blastomatosis
Syndrome	-	Beckwith-Wiedemann syndrome	16p12.2 deletion	-	WT-1 mutation
Procedure	NSS	NSS	NSS	NSS	NSS
NC-MRA scanning duration (min:sec)	04:50	03:55	03:55	04:50	03:28
Segmentation time (min)	29	41	34	73	28
Volume tumor segmentation (ml)	1.4	4.0	69.2	24; 17; 1.2; 0.3; 3.4; 11.6; 0.12	2.3
3Dprinting time (hours:min)	18:39	15:41	16:39	31:26	18:10
3Dprinting cost (€)	38	2.57	3.06	5.80	3.27

3.5 DISCUSSION

A combined imaging, (protocolled) segmentation and visualization workflow resulted in patient-specific 3D anatomical models for the preoperative planning of WT patients. The 3D visualization workflow aimed to help pediatric surgeons improve their understanding of anatomical relationships and orientation. Because of the preparation time of about 1 hour and a printing time of 20 hours, this 3D visualization workflow can be completed within a limited timeframe of two days between the preoperative MRI and surgery. Additionally, it is inexpensive as the head-mounted display costs 3000 euros and all software packages are open-source or self-developed. Limitations in previous studies on 3D modelling for WT, such as low image quality, long segmentation and long visualization processing. Wake et al. (2017) report a 3D printing cost per model of ± $1000 (US dollars), a segmentation time of +/- 7 hours and 3d printing time of ± 10 hours (13). Wellens et al. (2019) report an average cost of $400 USD per printed model and a segmentation and 3d printing manufacturing time of 4 to 5 days (12). In this pilot study, we have addressed these limitations through the development of our own innovative workflow in collaboration with the departments of pediatric surgery, radiology and 3D imaging specialists. The segmentation protocol of the workflow allowed for fast 3D modelling and the HoloLens proved to be a fast and useful visualization tool. Our 3D printing technique was slow (± 20 hours) because of the fine layer profile (0.1 mm thickness). Increasing the layer profile would decrease the printing time significantly. Our in-house 3D printer is limited in color and materials, yet it was sufficient quality, and with an average price of ± 3.50 euros and machine cost of 5500 euros it was considered a sustainable technique.

It is difficult to quantify the advantages of 3D anatomical models for the preoperative planning of NSS for WT. An increase in surgical confidence for NSS for WT has been shown retrospectively (12), but quantifying the advantage remains subjective (12). In adults, 3D printed renal models based on preoperative MRI scans could help during surgical decision making (6). Moreover, 3D printed models did allow adult surgeons to improve their translation from 2D CT and MRI data into 3D anatomical relationships, which appeared more relevant in smaller lesions (15). Although, the results from these studies may not be directly applicable to children because image quality is generally superior in adults (16), we expect that 3D printed models could help in the preparation of pediatric oncologic surgery. The clinical advantage of the described 3D visualization workflow for children may be quantified in the future. We need to understand how 3D modelling for

preoperative planning influences pediatric surgical decision-making and confidence in order to understand how these models benefit our patients.

The proposed workflow appears useful during the preparation of NSS for bilateral or syndromic WT patients. In unilateral non-syndromic patients, NSS is only performed in a very specific group of patients as controversies arise due to the inherent increased risk of positive surgical margins (3). Current figures report a positive surgical margin of the sparingly removed tumor masses (treated with the Children's Oncology Group protocol) between 15.7 % and 31 % (17,18). In accordance with the SIOP-RTSG Umbrella protocol, in the case of a positive surgical margin these young patients will need additional chemotherapy and possibly radiotherapy. In most cases it is unknown how these positive margins occurred. The 3D visualization workflow may help surgeons to better understand complicated pathologic and anatomic regions and give an improved insight on where and how these positive margins occur. Additionally, 3D modelling may assist during the difficult patient selection for NSS through an increased understanding of the patient's anatomy. This twofold advantage might lead to fewer positive surgical margins and improved oncological outcomes.

In order to achieve improved clinical outcomes, all anatomical structures require a high-fidelity 3D model. However, the segmentation of the veins and UCS remains a manual and problematic task. The overlay of the arterial segmentation helps to differentiate between arterial and venous vasculature. Currently, this technique is insufficient for the accurate segmentation of intraparenchymal veins, likely due to intrasequential movement. The UCS was difficult to segment, as the full extent of the UCS is generally difficult to appreciate with standard imaging. More specific non-contrast imaging techniques such as non-contrast enhanced MRVenography based on b-SSFP and MRUrography may help further improve the model quality and may speed up the segmentation. NC-MRV has the additional potential to allow for assessment of venous tumor thrombi (19). Nevertheless, the arterial model is considered to have the highest surgical value as this is the most relevant for NSS (4). For this reason, despite the low model quality of the veins and UCS, the overall models were considered to be of sufficient value and usability.

In addition to accurate segmentations, the visualization of patient-specific 3D models is paramount to how the models are understood. Augmented Reality visualization through a HoloLens offered a viable and fast technique for the visualization. A hologram is computed more easily and less costly in comparison to 3D printing. However, there is no consensus on whether there is a significant clinical

advantage to the use of AR instead of other visualization techniques such as 3D printing, 2D rendering on a computer monitor or volume-rendering. Previously, no significant difference between 3D visualization techniques (AR or 3D printing) was found for WT patient-specific models (12). However, we currently believe AR is the most desirable visualization technique due to the opportunity to develop Mixed Reality concepts. In the future, the HoloLens could allow intraoperative kidney-model matching. Mixed Reality models are used in adult laparoscopic renal surgery through registration of the 3D model with the laparoscopic image (7). With Mixed Reality, rigid matching through an anatomical landmark registration has been described for open visceral surgery (20). However, to the best of our knowledge, Mixed Reality for open renal surgery has not been described yet. In the context of NSS, this would allow the surgeon to get a sense of depth and infiltration of the tumor and superimposing vasculature could assist surgeons to determine the resection margins.

Our pilot study is limited by the lack of evaluation of these anatomical models. A subjective analysis through questionnaires was not performed. However, we aimed to use novel imaging and visualization techniques and implement them into clinical care. The technique has been improved and should be further evaluated through the prospective use of the aforementioned questionnaires. Additionally, the 3D models should be compared with the pathology specimens in order to quantify the accuracy of the 3D models.

In the future, we aim to implement and evaluate 3D imaging technology in pediatric oncologic surgery as standard of care and evaluate the added value. Additionally, we aim to develop more automated segmentation procedures for WT patients and work towards to use of intraoperative holograms through Mixed Reality.

3.6 CONCLUSIONS

This pilot study demonstrates how a strong collaboration between the pediatric surgery and radiology departments and 3D imaging specialists will help to shape the future of pediatric oncological surgery. A combination of specific high-resolution MRI sequences, protocolled segmentation techniques and AR visualization improved the visualization for the preoperative planning of pediatric renal tumors. This designed 3D visualization workflow is an easily implementable technique to help pediatric oncological surgeons prepare for nephron-sparing surgery in patients with Wilms' tumors.

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Chapter 4 Non-Contrast MRA as non-invasive vasculature imaging for pediatric renal tumor surgery, a pediatric surgical perspective

Authors

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4.1 ABSTRACT

Background

Surgical resection of renal tumors in children is an essential part of treatment. To reduce complications and improve surgical understanding of renal arterial vasculature, a high-resolution Non-Contrast MRA (NC-MRA) sequence was implemented. We retrospectively and prospectively assessed the use of NC-MRA for the preoperative planning of Wilms Tumor surgery.

Methods

The preoperative MRI scans of all kidney tumor patients between October 2019 and July 2021 were retrospectively assessed by two pediatric surgeons and one pediatric urologist. The surgeons assessed their understanding of the aorta, renal artery, extraparenchymal artery and intraparenchymal artery in the T2-Weighted sequence (T2W), Contrast-Enhanced MRA (CE-MRA) and NC-MRA. Moreover, they assessed whether the sequence helped them during the preoperative planning. All assessments were based on a 5-point scale. A Cumulative Link Mixed Model was used to model the correlation between the different anatomical regions, surgeons and MRI sequences. Additionally, the scans of 10 patients undergoing a surgical resection were assessed prospectively by one of the performing surgeons.

Results

For the retrospective assessment we included 37 patients. The median additional scan time for NC-MRA was 209 seconds. The NC-MRA visualized the intraparenchymal arteries more accurately than the CE-MRA (3 vs 1 out of 5). Moreover, there was no significant difference between the scoring of the NC-MRA and T2W at this anatomical region. The NC-MRA sequence was considered useful during surgical planning (4 out of 5) but there was no significant difference from the T2W sequence. During the prospective assessment, the NC-MRA helped the differentiation of vessels at the level of the intraparenchymal arteries and was therefore considered most useful for patients undergoing nephron-sparing surgery.

Conclusions

NC-MRA is considered a helpful additional imaging sequence for the preoperative planning of Wilms Tumor surgery, especially in nephron-sparing surgery.

4.2 INTRODUCTION

Five to six% of all pediatric malignancies comprise of a renal tumor of which 90% is a Wilms Tumor (WT). Treatment in Europe is in accordance with the International Society for Pediatric Oncology Renal Tumor Study Group (SIOP-RTSG) UMBRELLA protocol (1). In North America, the Children's Oncology Group uses the ARENA treatment protocol. Surgical resection is an essential part of treatment in both treatment protocols and is performed either through a total nephrectomy (TN) or nephron sparing surgery (NSS). Unfortunately, 18.4% patients experience one or more surgically related complications such as intraoperative tumor rupture, superior mesenteric artery injury and hemorrhage (2–4). In the case of NSS, positive surgical margins rates are as high as 15.7 – 36.4% and significantly impact the overall survival of these children (5–7). To reduce complications, further improvement of the preoperative surgical preparation and intraoperative surgical approach is required.

Preoperatively, Magnetic Resonance Imaging (MRI) is currently used in the UMBRELLA protocol for treatment response assessment and surgical planning. The anatomical sequences of MRI offer a 2D view of the patient anatomy. For the preoperative planning of NSS, detailed visualization of the small extra- and intraparenchymal arteries is essential (8,9). For TN, it is important to preoperatively assess accessory renal arteries. However, conventional anatomical T2- and T1-Weighted MRI sequences do not differentiate arterial and venous vasculature. It can be difficult to assess these structures separately, especially intertwined vessels. Computed Tomography Angiography (CTA) may be used to image these vessels with a higher resolution. However, this requires radiation, the use of potentially nephrotoxic contrast agents and a stressful scanning moment for these young patients. For these reasons, the radiology department in our institution together with the pediatric surgery department implemented a Non-Contrast Magnetic Resonance Angiography (NC-MRA) sequence for the visualization of renal arteries in children. This sequence, inflow-based balanced Steady State Free Precession (hereafter referred to as NC-MRA), offers high resolution imaging of the renal arteries with MRI. This sequence is specifically useful in a pediatric population (10–12).

The high resolution of NC-MRA allows surgeons to assess the intricate arterial vessels of the kidney to prepare for surgery. However, whether NC-MRA improves pediatric surgical understanding is still unknown. Therefore, we aimed to assess the value of NC-MRA on the preoperative understanding of arterial vasculature in pediatric renal

tumor patients in comparison to conventional T2W MRI and Contrast-Enhanced MRA.

4.3 PATIENTS AND METHODS

To evaluate the use of NC-MRA during preoperative planning of pediatric renal tumors, we retrospectively assessed the preoperative scans of patients since this sequence has been implemented in our center. Moreover, we included a prospective assessment in which a surgeon performed the same assessment of preoperative imaging prior to surgery. The institutional ethical board approved this study and waived the requirement for a separate informed consent.

4.3.1 Retrospective

For the retrospective assessment, patients with a renal tumor in the Princess Máxima Center for Pediatric Oncology between October 2019 and July 2021 were included. Inclusion criteria were pediatric age (<19 years), proven renal tumor and a complete imaging protocol prior to surgery. All patient data was anonymized.

4.3.2 Prospective

For the prospective assessment, 10 consecutive patients with a renal tumor in the Princess Máxima Center for Pediatric Oncology between July 2021 and February 2022 were included. Inclusion criteria were pediatric age (<19 years), radiologically proven renal tumor and preoperative imaging performed at the Princess Máxima Center.

4.3.3 Imaging

In accordance with the UMBRELLA treatment protocol, patients received a standard pediatric kidney tumor MRI protocol for the assessment of treatment response and preoperative surgical planning. The complete imaging protocol has been described in an earlier study (13). For this study, we used a 3D T2-Weighted (-W) sequence due to the high resolution and multiplanar reconstruction. The 4D Contrast-Enhanced MRA (CE-MRA) was included as this sequence allows for whole body dynamic arterial imaging. This CE-MRA was visualized with a radial 3D maximum intensity projection (MIP). NC-MRA was used for more specific imaging for renal vasculature. In comparison to CE-MRA, NC-MRA has a narrow field of view but a higher resolution. 2D transversal, coronal, and sagittal MIPs of NC-MRA were included. Surgeons were allowed to assess these sequences as well as the MIPs of both MRA scans in any plane in any order.

4.3.4 Surgical assessment

Surgical assessment was performed by one oncologic pediatric surgeon (C.P.V., 23 years of experience), one oncologic pediatric surgeon in training (G.M.J.B., 2 years of experience) and one pediatric urologist (A.J.K., 30 years of experience). Retrospective imaging was available to the surgeon in the open-source medical image viewer Horos version 4.0.0 (www.thehorosproject.org). The Sectra IDS7 Picture Archiving and Communication System (PACS) Workstation (Sectra Workstation Version 22.1, Sectra AB, Sweden) was used for the prospective assessment. Surgeons were asked to assess how the provided imaging helped them understand four anatomical regions during a preoperative setting: aorta, renal artery, extraparenchymal arteries (hilar region) and intraparenchymal arteries. The surgeons assessed the vasculature of the kidney with tumor. In case of bilateral disease, both sides were assessed. Surgeons rated their anatomical understanding based on a 5-point scale (1 = very poor, 2 = poor, 3 = fair, 4 = well, 5 = very well). Moreover, the surgeons were asked whether the provided imaging was of added value for preoperative planning. This was also based on a 5-point Likert scale. The anatomical region of the aorta and the value for preoperative planning was scored per patient. The anatomical region of the renal artery, extraparenchymal artery and intraparenchymal arteries were scored per kidney.

4.3.5 Statistical Analysis

Statical analysis was performed in RStudio for MacOS version 1.4.1717 (RStudio, Boston, Massachusetts, United States). For the retrospective analysis, a cumulative link mixed model was used to account for the ordinal measurements repeated per patient. The model contained a normalized score as the outcome variable, with fixed effects of anatomic region, and MRI sequence and a two-way interaction between the anatomical region and the MRI sequence. Moreover, a random effects structure for each patient was used. This model allowed to determine significant factors contributing to the differences in scoring by the surgeons.

The prospective data was described through descriptive statistics (mean and standard deviation).

4.4 RESULTS

4.4.1 Patient population

The retrospective assessment included 35 patients (17 female, 19 male). The patients had a median age of 42 (5-106) months at the time of surgery. Three patients had bilateral disease thus 38 kidneys were included in the assessment of the renal artery, extraparenchymal arteries and intraparenchymal arteries. The additional median scanning time required for NC-MRA was 3 minutes and 39 seconds. Figure 4-1 depicts the MIP in both the transversal and coronal plane of a 4-year-old patient. The abdominal vasculature is visualized with a high resolution of 0.5x0.5x1 mm. Furthermore, the small coronal length of the field of view can be observed.

Ten patients were included in our prospective surgical assessment. The patients had a median (min-max) age of 52.5 (20-178) months at the time of surgery. All patients in the prospective cohort presented with an unilateral unifocal tumor, no patients presented with bilateral or multifocal disease.

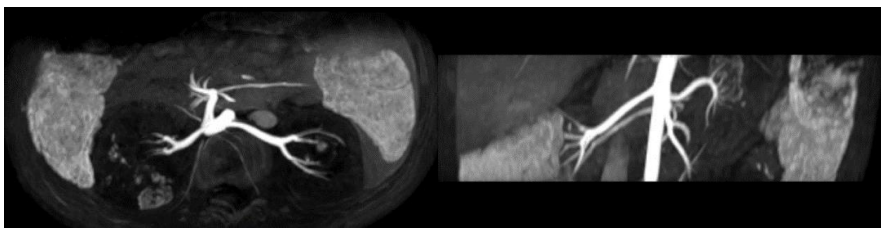

Figure 4-1 shows a representative transversal (left) and coronal (right) 2D maximum intensity projection of NC-MRA of a 4-year-old patient. This sequence visualizes the aorta, renal arteries, extra- and intraparenchymal arteries.

4.4.2 Retrospective surgical assessment

The descriptive results of the retrospective surgical assessment are shown in Table 4-1. The estimated means and confidence intervals of the cumulative linked mixed model per patient (Figure 4-2A) and per kidney (Figure 4-2B) are shown in Figure 4-1. The significance of the differences between the three different sequences for the anatomical regions were determined through a pairwise comparison of the estimated means and are shown in Table 4-2.

The cumulative linked mixed model showed a lower estimated mean and confidence interval for the CE-MRA for the extra- and intra-parenchymal arteries and value for preoperative planning in

comparison to the other two sequences. The T2-W sequence and NC-MRA sequence showed an insignificantly different estimated mean and confidence interval at all anatomical regions except for the renal artery. The NC-MRA had a slightly lower estimated mean in comparison to the T2-W sequence for this anatomical region as shown by the model.

The anatomical overview of the T2-W sequence helped during the preoperative planning, thus making it more useful for general cases. CE-MRA was not considered helpful for anatomical understanding nor helpful for preoperative planning. NC-MRA seemed to help more specifically to determine the exact location of segmental branches.

Table 4-1 Results of the retrospective assessment for all three sequences for all anatomical regions for three observers.

Retrospective assessment Mean ± SD	**T2-W**	**CE-MRA**	**NC-MRA**
Aorta	4.9 ± 0.54	5.0 ± 0.20	4.9 ± 0.38
Renal artery	4.8 ± 0.61	4.2 ± 1.07	4.4 ± 1.06
Extraparenchymal artery	3.8 ± 1.41	3.0 ± 1.33	3.6 ± 1.38
Intraparenchymal artery	2.9 ± 1.61	1.5 ± 0.82	2.6 ± 1.42
Value for preoperative planning	3.7 ± 1.30	2.8 ± 1.19	3.7 ± 1.22

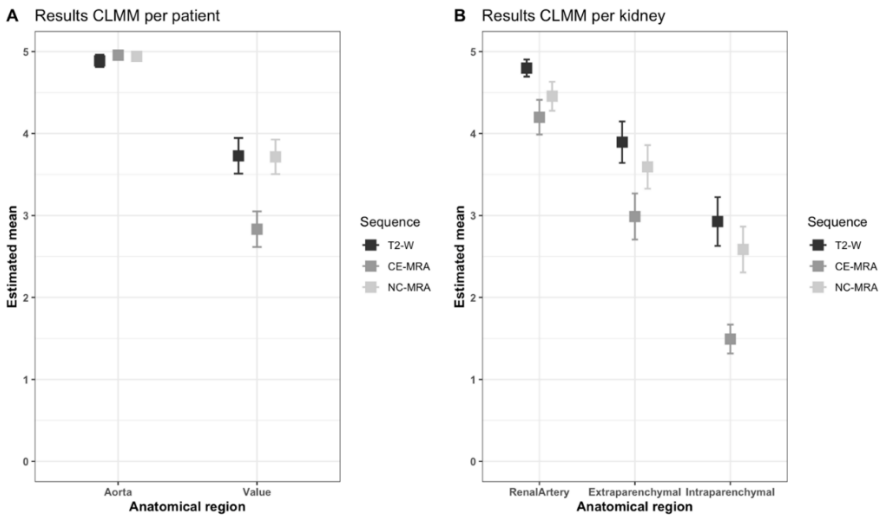

Figure 4-2 shows the estimated means and confidence intervals (0.95) of the used cumulative link mixed model. A visualizes the results per patient for the anatomical region of the Aorta and the value for preoperative planning. B shows the results per kidney for the anatomical region of the Renal artery,

Extraparenchymal artery and Intraparenchymal artery. T2-W sequence is depicted in black, CE-MRA in dark gray and NC-MRA in light gray.

Table 4-2 Pairwise comparison of the estimated means from the cumulative link mixed model corresponding to Figure 4-2 between the three different sequences for the anatomical regions.

	Sequence		**Estimated difference**	**P-value**
Aorta	T2-W	-CE-MRA	-0.075	0.69
	T2-W	- NC-MRA	-0.053	0.88
	CE-MRA	- NC-MRA	0.017	0.99
Renal artery	T2-W	- CE-MRA	0.577	<.001
	T2-W	- NC-MRA	0.320	0.05
	CE-MRA	- NC-MRA	-0.257	0.57
Extraparenchymal	T2-W	- CE-MRA	0.922	<.001
artery	T2-W	- NC-MRA	0.302	0.70
	CE-MRA	- NC-MRA	-0.620	0.01
Intraparenchymal	T2-W	- CE-MRA	1.344	<.001
artery	T2-W	- NC-MRA	0.272	0.89
	CE-MRA	- NC-MRA	-1.072	<.001
Value for preoperative	T2-W	- CE-MRA	0.913	.001
planning	T2-W	- NC-MRA	0.168	.00
	CE-MRA	- NC-MRA	-0.880	.001

4.4.3 Prospective surgical assessment

The results of the prospective surgical assessment are shown in Table 4-3. The NC-MRA sequence scored higher or equal for the visualization of the anatomical regions yet scored lower in value for preoperative planning in comparison to the T2-Weighted sequence.

Table 4-3 Results of the prospective assessment performed by surgeons prior to surgery for all three sequences for all anatomical regions.

Prospective assessment Mean ± SD	**T2-W**	**CE-MRA**	**NC-MRA**
Aorta	4.6 ± 0.97	4.8 ± 0.42	4.9 ± 0.32
Renal artery	4.4 ± 0.84	4.1 ± 1.20	4.7 ± 0.68
Extraparenchymal artery	3.7 ± 1.51	3.4 ± 1.35	3.9 ± 1.29
Intraparenchymal artery	3.4 ± 1.51	2.5 ± 1.51	3.4 ± 1.43
Value for preoperative planning	4.6 ± 0.70	3.0 ± 1.25	3.3 ± 1.34

There was an observable difference between the two datasets. NC-MRA scored lower in a prospective setting for the value for intraoperative planning. Coincidentally, the visualization of the intraparenchymal arteries in the CE-MRA was scored higher in the prospective dataset, yet this did not seem to cause a large difference in usefulness for preoperative planning.

4.5 DISCUSSION

The collaboration between radiology and surgery is becoming ever more important for the preoperative planning of pediatric oncologic surgery. The implementation of NC-MRA by the radiology department specific for the purpose of preoperative planning of renal tumors showed to be useful and aid arterial understanding of surgeons. NC-MRA visualizes arterial structures with a white on black contrast, which offers distinct additional features to the anatomical high resolution T2-W imaging. Moreover, it proved to be significantly more useful than the more conventional CE-MRA for preoperative planning. NC-MRA does not replace the CE-MRA and is considered an additional sequence specific for this application.

The use of non-contrast MRA in children for the evaluation of renal vasculature prior to a partial or total nephrectomy was first described in 1994. In this series of 4 patients phase-contrast MRA was found sufficient and reduced the need for invasive imaging techniques (14) In a later pediatric study using NC-MRA, the image quality of the extraparenchymal arteries was rated good and intraparenchymal arteries as acceptable by two radiologists (11). However, these patients were significantly older than our cohort and did not have renal tumors. In patients younger than 4 years, NC-MRA was used to detect crossing renal vessels showing a high correlation with intraoperative findings (15). Our study specifically looked at the value of NC-MRA for surgical

planning in comparison to conventional imaging techniques with similar positive results.

NC-MRA is easily implementable for all WT patients, as the patient systematically receives MRI for treatment response assessment and the additional scan time is considered relatively short (median scan time was 3 minutes and 39 seconds). NC-MRA is specifically considered useful for the preoperative planning of nephron-sparing surgery. Here preoperative understanding of the intraparenchymal arteries is essential to determine the resection margin (16). Earlier we relied on CTA for the imaging of these small arterial vessels. Yet since the implementation of NC-MRA, CTA is only rarely performed. Moreover, we did not perform a comparison study between NC-MRA and CTA. The required additional radiation dose of CTA for these children was not considered proportionate for this purpose. For WT patients needing a total nephrectomy, arterial understanding is not a key component of the preoperative plan. Most components can be observed in the T2-W or T1-W anatomical sequences. This also explains the observed improved understanding of the intraparenchymal arteries of the CE-MRA in the prospective dataset in comparison to the retrospective dataset yet this did not result in an increased value for preoperative planning for this sequence. However, the observing surgeons noted that for TN, NC-MRA can help understanding the hilar region, position of the adrenal artery and accessory renal arteries. The sequence therewith attributes to the confidence of the surgeon performing TN in a small yet significant way.

To further improve preoperative patient-specific understanding, 3D modelling may also be used. This novel imaging technique helps to understand patient-specific anatomical relationships. CTA is typically used for 3D modelling (17,18) yet this imaging technique is undesirable in children. Current MRI-based 3D modelling approaches are limited by the imaging resolution and arterial visualization (19–21). Using NC-MRA for high resolution arterial imaging may help overcome these limitations of MRI. This sequence allows for high fidelity 3D models in most WT patients requiring NSS (13). This way no radiation nor additional scanning moment is needed to compute high fidelity 3D models to be used for preoperative planning.

The results of this study are shaped by its limitations. First, since NC-MRA was not compared with the gold standard CTA, the radiological accuracy of NC-MRA remains unclear for our patient cohort. Secondly, in theory, there could have been a learning effect during the assessments as the surgeons assessed all MRI scans. This effect was not accounted for in the statistical model. Thirdly, the retrospective and prospective assessments were largely performed by different observers and did not allow for a direct quantitative comparison of both groups.

In the future, we hope to increase the application of this specific MRI sequence in different aspects of pediatric oncologic surgery. NC-MRA could be useful in surgery of neuroblastoma encasing the peritoneal vasculature. For hepatoblastoma patients, non-contrast imaging may help to reduce the amount of four-phasic CTs currently used for preoperative planning.

4.6 CONCLUSION

NC-MRA is a useful and harmless technique for the imaging of arterial vasculature to be used for the preoperative planning for patients with Wilms' tumors. The sequence improves the understanding of renal vasculature in comparison to CE-MRA and is easily implemented in the current treatment protocols possibly limiting the need for preoperative CTA.

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Chapter 5 Virtual Resection: A New Tool for Preparing for Nephron-Sparing Surgery in Wilms Tumor Patients

This chapter is based on

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5.1 ABSTRACT

Nephron-Sparing surgery (NSS) in Wilms tumor (WT) patients is a surgically challenging procedure used in highly selective cases only. Virtual resections can be used for preoperative planning of NSS to estimate the remnant renal volume (RRV) and to virtually mimic radical tumor resection. In this single-center validation study, virtual resection for NSS planning and the user experience were evaluated. Virtual resection was performed in nine WT patient cases by two pediatric surgeons and one pediatric urologist. Pre- and postoperative MRI scans were used for 3D visualization. The virtual RRV was acquired after performing virtual resection and a questionnaire was used to assess the ease of use. The actual RRV was derived from the postoperative 3D visualization and compared to the derived virtual RRV. Virtual resection resulted in virtual RRVs that matched nearly perfectly with the actual RRVs. According to the questionnaire, virtual resection appeared to be straightforward and was not considered to be difficult. This study demonstrated the potential of virtual resection as a new planning tool to estimate the RRV after NSS in WT patients. Future research should further evaluate the clinical relevance of virtual resection by relating it to surgical outcome.

5.2 INTRODUCTION

Wilms tumor (WT), also known as nephroblastoma, is the most frequently occurring renal tumor in children with a five-year survival rate of ~90% (1–3). Approximately 35 children are diagnosed with WT in the Netherlands annually and in most cases this is an unilateral tumor. In 5-10 % of WT patients, the disease is bilateral with an increased likelihood for end-stage renal disease and secondary morbidity (4). Treatment of WT is in accordance with the Umbrella treatment protocol prescribed by the Renal tumor Study Group of the International Society of Pediatric Oncology (SIOP-RTSG) (5). This treatment protocol describes neoadjuvant chemotherapy, followed by open radical or partial nephrectomy, also known as nephron-sparing surgery (NSS), and adjuvant chemotherapy. The preferred surgical treatment in bilateral and syndromic unilateral patients is NSS with radical resection of the tumor to preserve as much functional remnant renal volume (RRV) as possible.

In nonsyndromic patients, radical nephrectomy is the standard of care and NSS is limited to certain patients who meet the criteria established in the SIOP-RTSG Umbrella treatment protocol 2016. These criteria should prevent worse oncological outcome due to irradical resection (R1 or R2) that upstages the tumor and implies the addition of radiotherapy (6). However, NSS may reduce the risk of end-stage renal failure and allow for more surgical treatment options in case of a metachronous tumor in the contralateral kidney (7). NSS cases require extensive preoperative planning to ensure a safe oncological outcome and the preservation of functional RRV.

For the preoperative planning of NSS, three-dimensional (3D) visualization is routinely used in the Princess Maxima Center. The introduction of this technique improved the anatomical orientation of surgeons performing oncologic renal surgery (8–11). In addition, Isotani et al. showed that 3D visualizations could be used for virtual resection of renal tumors in adults (12). This technique allows surgeons to virtually perform NSS and estimate the RRV preoperatively. However, this technique has not been implemented in pediatric oncologic surgery yet. In this study, a method for virtual resection planning of NSS for WT patients and the user experience of virtual resection are evaluated by the surgeons.

5.3 MATERIALS AND METHODS

In this single-center study, the feasibility of virtual resection was examined as an additional tool for preoperative NSS planning for WT

patients using retrospective acquired imaging data. 3D visualizations were prepared with the in-house developed 3D imaging workflow for NSS developed by Fitski et al. (13). Additionally, the actual RRV of the patient was computed after 3D visualization of the available postoperative magnetic resonance imaging (MRI) scans. Secondly, virtual resections were performed by two pediatric surgeons and one pediatric urologist. Thirdly, the derived virtual RRVs were compared with the actual RRV resulting in a volume fraction. Finally, surgeons were asked to complete a questionnaire to assess the user experience of virtual resection in terms of technical performance and clinical relevance.

5.3.1 Patient inclusion

This study was performed using retrospective imaging data of WT patients who underwent NSS and received both a pre- and postoperative MRI in the Princess Maxima Center in The Netherlands between 01/01/2019 and 01/07/2021. All NSS patients received standard care in accordance with the SIOP-RTSG UMBRELLA treatment protocol 2016. Within this protocol, patients received preoperative MRI and if the tumor was pathologically characterized as high risk, postoperative MRI was also performed. Twelve patients were considered for NSS during this period. In six patients, the tumor was pathologically characterized as high risk, and postoperative MRI was performed. Of these six patients, three had surgery on both kidneys, which resulted in nine single operative cases. The Institutional Ethics Review Board waived the necessity of informed consent since the study did not involve the actual patients and treatment was not influenced. All patients were included in the UMBRELLA protocol and signed the UMBRELLA patient information form.

5.3.2 Imaging and 3D-visualization

All patients were scanned, under sedation, with a 1.5 tesla MRI system (Achieva, Philips Medical Systems, Best, The Netherlands). In addition, 3D visualizations were performed with the acquired MRI scans in the 3D Slicer (version: 4.11.20210226) software package (14). To determine the actual RRV a post-contrast fat-suppressed T1-Weighted MRI sequence was used in accordance with the visualization protocol developed by Fitski et al. (13).

5.3.3 Virtual Resection

Virtual resection was performed by two pediatric surgeons and one pediatric urologist with extensive experience in NSS. For the virtual resection, an open-source extension was used in 3D Slicer: ResectionPlanner. To get familiar with the system and virtual resection, the surgeons performed a training case.

The surgical protocol for NSS consists of identifying the tumor with intraoperative ultrasound, followed by circumscribing the resection border with diathermy, and subsequent radical tumor removal (15). The virtual resection was designed to mimic this surgical approach. The methodology for virtual resection is visualized in Figure 5-1. The surgeon was able to get familiar with the patient's anatomy by inspecting the 3D visualization and the available imaging data beforehand. After inspection, resection started with the surgeon selecting several points on the surface of the kidney and the resection software computed a closed curve between these points. This closed curve is visualized with the purple line in Figure 5-1A and represents the circumscription of the resection border with diathermy. Secondly, the surgeon selected several intraparenchymal points in the available imaging data (shown in Figure 5-1B). Both the closed circle and intraparenchymal points were combined and used as input for the ResectionPlanner. This resulted in a 3D model of the virtual remnant kidney used for the computation of the virtual RRV shown in Figure 5-1C. Finally, the surgeon was able to make small final corrections on the 3D model with tools available in 3D Slicer.

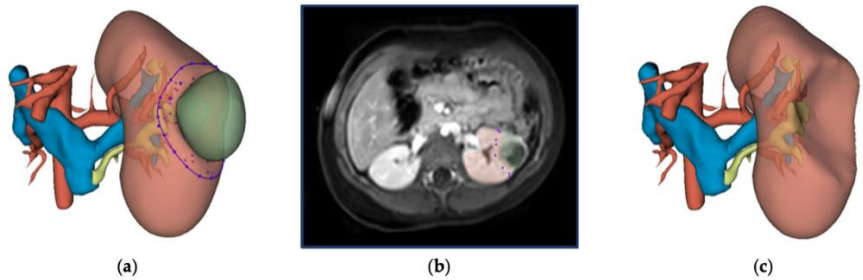

Figure 5-1 Workflow for virtual resection in 3D Slicer: (**A**) 3D visualization of the kidney, tumor, urinary collecting system, renal artery and renal veins. The closed curve as selected by the surgeon is indicated in purple. (**B**) Preoperative MRI imaging (post-contrast fat-suppressed T1-weighted) of the abdomen with the kidney and WT segmentation in red and green, respectively. The surgeon selected intraparenchymal points on this MRI scan. (**C**) 3D visualization of the virtual kidney volume after virtual resection.

5.3.4 Volumetric Assessment

The performance of virtual resection was evaluated with the agreement of the virtual RRV and the actual RRV by computing a volume fraction. The volume fraction was computed by dividing the virtual postoperative kidney volume by the actual postoperative kidney volume (equation 2). Ideally, the virtual resection volume matches perfectly with the actual postoperative volume resulting in a volume fraction of 1.0. A volume fraction >1.0, implies less volume got resected by virtual resection than during the actual surgery and thus the virtual RRV is overestimated compared to the actual RRV. Underestimation, volume fraction < 1.0, implies more volume got resected by virtual resection than during the actual surgery.

$$\text{Volume fraction} = \frac{V_{\text{postoperative, virtual}}}{V_{\text{postoperative, actual}}} \quad (1)$$

5.3.5 User Experience

The surgeons were asked to complete an in-house developed questionnaire. Each statement was scored on a Likert-scale from 1 up to 5 ranging from 'strongly disagree' (1) to 'strongly agree' (5). The questionnaire contained six statements. Two of the statements measured the technical performance as experienced by the surgeon: S1 and S4. Four of the statements evaluated the clinical relevance: S2, S3, S5 and S6.

5.3.6 Statistics

All statistical analyses were performed using SPSS Statistics Version 27 (IBM Corp., Armonk, NY, USA). For the volumetric assessment, the median and the interquartile range (IQR) were computed. For the user experience analysis, answers per statement per surgeon were collected and the median and the interquartile range (IQR) were determined.

5.4 RESULTS

5.4.1 Patient Characteristics

The six patients had a mean age of 48 months (STD = 32 months). The complete pre- operative 3D visualization was successfully obtained with MRI data only in 7 of the 9 cases. In cases eight and nine, 3D visualization of the kidney and tumor were obtained from

preoperative MRI. However, the vascular system and the urinary collecting system (UCS) were obtained from computed tomography. Subsequently, the 3D models were accurate, manually matched with the 3D models derived from the preoperative MRI. Patient demographics, tumor characteristics and the time between NSS and acquisition of the postoperative scan are described in Table 5-1.

Table 5-1 The patient demographics, tumor characteristics and the time between the scans and surgery are listed for the nine operative cases. The superscripts imply the same patient resulting in two single operative cases.

Case	**1***	**2**	**3**	**4**	**5***	**6‡**	**7‡**	**8Ψ**	**9Ψ**
Gender (M/F)	F	M	F	F	F	M	M	M	M
Age (months)	06	14	41	40	106	0	30	54	54
Disease	UF	UF	UF	UF	UF	UF	UF	MF	UF
Location	Left	Left	Left	Right	Left	Left	Right	Left	Right
Position	LP	UP	MP	MP	UP	LP	LP	LP and MP	MP
Syndrome	-	BWS	-	WT-1	-	-	-	BWS	BWS
Time between NSS and acquisition of the postoperative scan (days)	20	187	65	126	35	48	48	386	48

M = male, F = female, UF = unifocal, MF = multifocal, UP = upper pole, MP = mid pole, LP = lower pole, BWS = Beckwith-Wiedemann Syndrome, WT-1 = Wilms tumor 1 mutation

5.4.2 Volumetric Assessment

Radical tumor resection was performed in all cases in both the actual and virtual resection. The actual and virtual postoperative volumes are visualized in Figure 5-2A. Most of the results are located near the black line which implies a volume fraction equal to one. In case eight, the tumor volume was three times larger than the kidney volume and a large resection was required. For this large resection, minor deviations in the surgical approach by the different surgeons caused a large difference in RRV among the surgeons and a relatively low volume fraction. In case nine, four additional tumor resections were performed next to the two tumors that were seen in preoperative MRI scans. This resulted in an overestimation of the virtual RRV. The volume fractions derived by each surgeon are visualized in Figure 5-2B and shown in Table 5-2. Based on the RRVs given in Table 5-2, the agreement among

observers appears acceptable. The median volume fraction was found to be 0.94 (IQR = 0.16).

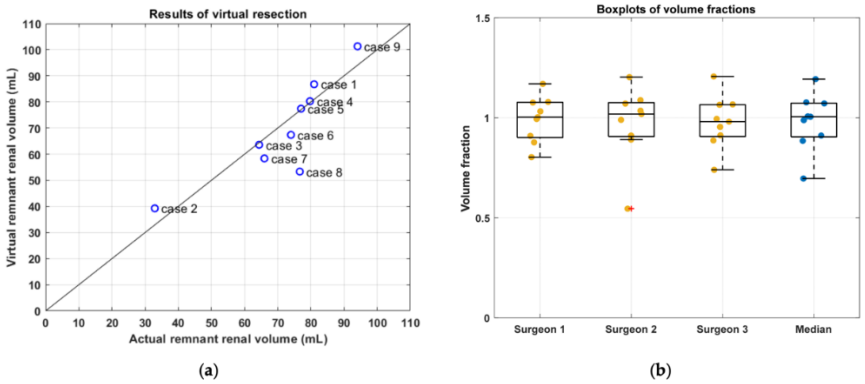

Figure 5-2 Results of virtual resection. In (**A**), the average virtual and the actual postoperative volume per case are shown. The black line implies a volume fraction equal to one, which corresponds to perfect agreement between the virtual and actual postoperative volume. In (**B**), the volume fraction per case is shown per surgeon and the median.

Table 5-2 The RRVs per surgeon for all nine operative cases.

	Surgeon 1	**Surgeon 2**	**Surgeon 3**
Case 1	97.42	98.16	96.84
Case 2	94.51	91.86	94.77
Case 3	91.65	92.08	90.84
Case 4	99.98	99.68	92.16
Case 5	98.23	96.74	95.87
Case 6	99.88	99.69	99.99
Case 7	99.47	97.97	99.03
Case 8	34.44	50.71	46.71
Case 9	94.57	93.54	92.73

5.4.3 User Experience

The results of the questionnaire are summarized in Table 5-3. Virtual resection was not considered difficult and the surgeons found virtual resection straightforward. No clear opinion was derived for the usefulness of the derived line of resection in the intraoperative decision-

making. There was a large variation between surgeons on whether the real-life surgical tumor resection was considered difficult.

Table 5-3 Results of the questionnaire were filled in by each surgeon. The results represent the patient cumulative opinion per statement. The table visualizes both the opinion per clinician as well as the median outcome.

Statement	Median	IQR
1. The virtual resection as performed in 3D Slicer was straightforward.	4.0	1.5
2. The derived line of resection, as created in 3D Slicer is useful in the intraoperative decision-making.	3.0	1
3. This virtual resection gives a better insight into other critical anatomical structures in addition to the standard preoperative 3D planning.	3.0	1
4. I classify this virtual resection, as performed in 3D Slicer, to be difficult.	1.0	1.5
5. Virtual resection, as performed according to this protocol, affects my intraoperative decision.	2.0	1
6. I expect this real-life surgical tumor resection, in this particular case, to be difficult.	2.0	2.5

5.5 DISCUSSION

This study evaluated virtual resection as a novel method to mimic tumor resection and estimate the RRV in WT patients. With virtual resection, surgeons can estimate the postoperative RRV with a nearly perfect matching volume fraction. Moreover, surgeons found the technique straightforward and not difficult. These features allow implementation in the current NSS planning to be feasible.

Comparable work of virtual resection in renal malignancies has been conducted in adults. Isotani et al. showed a significant correlation between the actual RRV and the virtual RRV based on the postoperative weight of the specimen (12). Using the volume of the specimen, instead of the postoperative MRI that is not routinely performed in every patient, allows for the inclusion of more patients in further prospective research. Ueno et al. showed that virtual resection allowed for accurate estimation as to whether the UCS had to be opened (16). The addition of the UCS in 3D visualizations could improve the orientation of critical anatomical structures of virtual resection and therewith the clinical relevance of virtual resection.

Intraoperative decisions may deviate from the planned resection based on preoperative imaging. Such differences between the

virtual resection planning and the actual performed surgery were found in several cases. In case 9, six lesions were found intraoperatively and resected, of which four lesions were not visible on preoperative imaging and therefore not included in virtual resection. Apparently, not all lesions appear visible in preoperative MRI scans that result in a deviation of the planned resection. In cases 6 and 7, an increase in the actual postoperative renal volume was found in comparison with the actual preoperative renal volume, suggesting postoperative growth of the kidney. Postoperative growth can be explained by hypertrophy because of postoperative adaptations in the kidney (17). In addition, postoperative hydronephrosis may also contribute to the increase in postoperative renal volume. To correct for postoperative growth, comparison with the contralateral kidney volume may allow for a more accurate estimation of the actual RRV. This may further improve the validation of virtual resection.

The clinical relevance of virtual resection must be evaluated before virtual resection influences the surgical approach in pre- and intraoperative decision-making and is implemented in current NSS planning. In this study, using the closed curve on the kidney's surface was found to be clinically relevant by one of the surgeons. This surgeon reported that intraoperative circumscription of the tumor would be less complicated after determining the closed curve virtually. Nevertheless, results from the questionnaires showed that the clinical relevance of virtual resection for these nine cases was deemed limited as all surgeons were familiar with all cases. In further research, virtual resection needs to be performed before the actual surgery to fully assess its clinical value on intraoperative decisions by pediatric surgeons. The clinical usability of virtual resection may be improved by adding more estimation features than solely the reduction in renal volume. Correlating renal function and RRV may result in a more accurate estimation of postoperative outcome than RRV alone (18,19). Secondly, virtual resections can be used to predict possible surgical complications such as urine leakage or a positive surgical resection margin (20).

Based on virtual resection, the postoperative RRV can now be estimated, which can be used for the indication of hemodialysis or chronic peritoneal dialysis catheters. Moreover, virtual resection provides an estimation of the opening of the UCS and therefore the indication for a double J catheter [12,16]. Thus, knowledge of the expected RRV and postoperative renal function, next to the preoperative clinical status, can influence decisions concerning the indication of dialysis catheters during NSS for acute renal failure.

This study has some limitations that need to be acknowledged. This was a single center study using retrospective acquired imaging data

of patients that already underwent NSS and thus the surgeons were familiar with all of the cases. Therefore, the clinical relevance rated by the surgeons could be affected. Second, only a limited number of cases were available for inclusion due to the requirements of both pre- and postoperative MRI. More patients can be included in further research when using a volumetric assessment of pathological specimen instead of the limited available postoperative MRI (12). Further research of virtual resection in combination with renal function and surgical complications is required to validate and strengthen the clinical relevance of this potential new tool for NSS planning.

5.6 CONCLUSIONS

This study demonstrated the potential of virtual resection as a new planning tool to estimate the RRV after NSS in WT patients. Virtual resection appeared to be a straightforward technique that is not difficult to use, hence implementing virtual resection in current NSS preoperative planning seems feasible. Future research should evaluate the added clinical value of simulating tumor resection during preoperative planning and incorporating surgical outcome, such as renal function and the indication for hemodialysis or chronic peritoneal dialysis catheters, additional to estimating RRV, to further validate and strengthen the clinical relevance of virtual resection as a new tool in NSS planning.

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Chapter 6 Patient-specific hydrogel phantoms for the preoperative simulation of nephron-sparing surgery in Wilms' tumor patients: a feasibility study

This chapter is based on

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6.1 ABSTRACT

Nephron-sparing surgery (NSS) for Wilms Tumor patients has a positive surgical margin rate of 15.7 – 36.4%. Innovative approaches may reduce the occurrence of positive surgical margins in NSS and prevent these children from having additional radiotherapy and chemotherapy. The feasibility of performing mock surgery on patient-specific hydrogel phantoms of the kidney, tumor, and arterial vasculature for preoperative simulation of NSS was assessed in two patients.

The development of patient-specific phantoms allowed the surgeon to practice surgery. Moreover, phantom specimens were assessed using MRI to understand the location and size of the smallest surgical margin. Surgeons reported that simulation surgery helped perform NSS safely and improved intraoperative tumor localization and resection planning.

The technique is considered feasible and useful when preparing for NSS. In the future, this technique may further help to achieve negative surgical margins in NSS and may also allow the use of NSS in patients typically regarded as ineligible for this procedure.

6.2 INTRODUCTION

Wilms Tumor (WT) is the most frequent occurring renal tumor in children. Patients in Europe are treated in accordance with the International Society for Pediatric Oncology Renal Tumor Study Group (SIOP-RTSG) UMBRELLA 2016 protocol (1). Surgical treatment consists of two different procedures, either through a total nephrectomy or NSS. Total nephrectomy is indicated for unilateral non-syndromic WT patients to ensure oncologic safety. Bilateral tumor patients and patients with a predisposition syndrome are surgically treated, if possible, with NSS to preserve renal function. Unfortunately, in the case of NSS, positive surgical margin rates are as high as 13.3 – 36.4% and this has significant impact on the overall survival of these children (2–5). Even with the use of intraoperative ultrasound (US) to prevent positive margins, the rate is still too high. In most cases it is unknown how and where these positive surgical margins occurred. They may be due to the difficult translation and interpretation of intraoperative US (6). Therefore, innovative techniques for further improvement of surgical guidance are required. The goal is to reduce the amount of positive surgical margins in NSS, improve outcome and prevent radiotherapy.

Three-dimensional (3D) imaging technology may help to understand where positive surgical margins occur through improvement of the understanding of patient-specific anatomical relationships. A combination of 3D imaging and 3D printing also allows for the creation of high-fidelity patient-specific hydrogel kidney tumor phantoms (7–9). The hydrogel phantoms are fit for surgical resection and contrast agents in the hydrogel allow for imaging compatibility (10). Arterial vasculature can be simulated either through additional hydrogel casting or 3D printing. The accurate positioning of the arterial vasculature in these phantoms is crucial as these vessels partially determine the size of the margin during NSS (11).

We have implemented this technique to create patient-specific hydrogel kidney tumor phantoms with arterial vasculature prior to planned surgery. In this feasibility study, we present the use of patient-specific hydrogel phantoms for the preoperative simulation in two WT patients undergoing NSS.

6.3 MATERIALS AND METHODS

Patients <19 years of age, treatment according to the UMBRELLA SIOP-RTSG 2016 protocol, with a radiologically proven renal tumor eligible for NSS and with available preoperative computed tomography (CT) or magnetic resonance imaging (MRI) scans two weeks prior to

surgery, were included. A schematic overview of the workflow for this study is given in Figure 6-1.

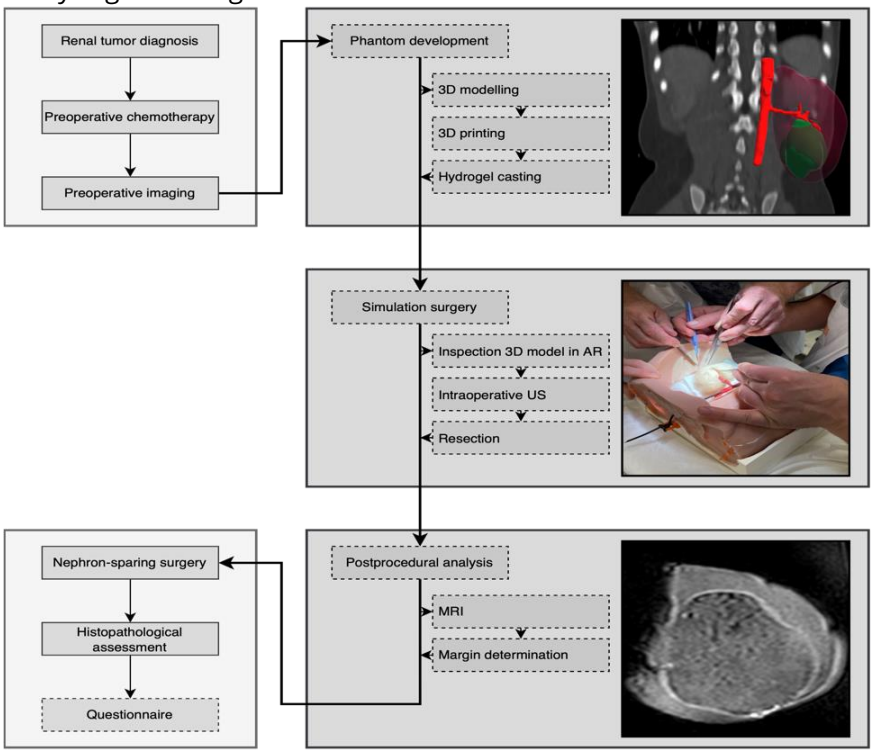

Figure 6-1 Schematic overview of the workflow used in this case series. The included pictures correspond to patient 1. The simulation consists of three parts: phantom development, simulation surgery and postprocedural analysis. Clinical care is continued according to the treatment protocol. AR = Augmented reality with a HoloLens 2

—— clinical care

- - - - simulation procedure

6.3.1 Phantom development

The production technique of the hydrogel phantoms was designed based on the work of Melnyk et al. (2020) (9). We describe three phases for production: the segmentation phase, the 3D printing phase and hydrogel casting phase. In Figure 6-2, the technique of production is visualized.

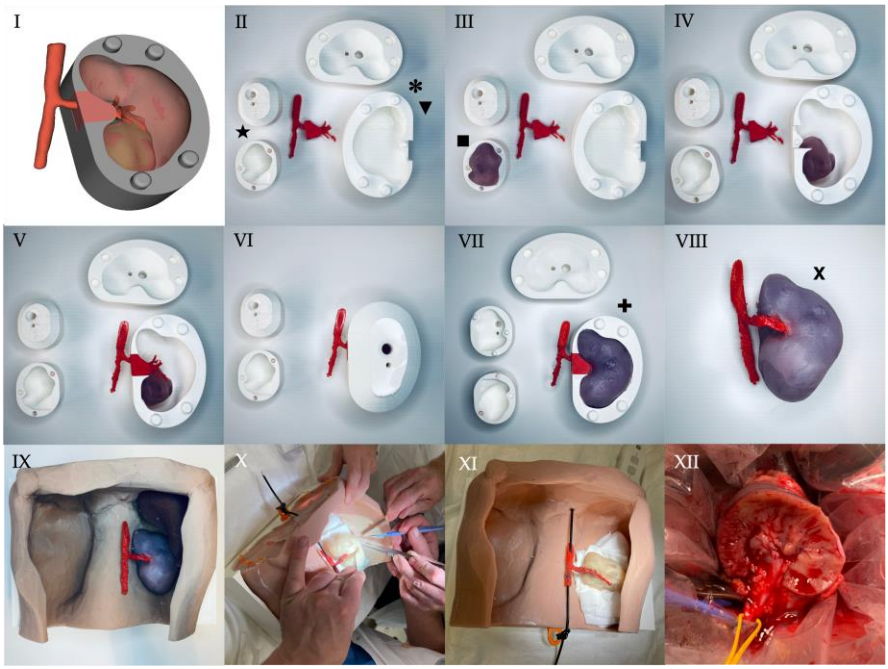

Figure 6-2 The steps of the 3D printing and hydrogel casting phase to produce the patient-specific phantom of patient 1 including postoperative images of the simulation and actual surgery. I: Digital overview of the kidney and tumor within the casting mold. II: The 3D printed casting mold of the kidney (✻), casting mold of the tumor (★) and arterial inlay (▼). III: Hydrogel tumor (■). IV: Hydrogel tumor positioned in the kidney casting mold. V: Arterial inlay positioned in the kidney casting mold. VI: Closure of the kidney casting mold with the hydrogel tumor and arterial inlay. VII: Hydrogel kidney and tumor with arterial inlay (✚). VIII: Complete patient-specific phantom after removal of the inlay material (**X**). IX: The patient-specific phantom positioned in the abdominal cavity of the pediatric abdominal silicone phantom. X: Performing simulation surgery on the patient-specific phantom. XI: Postoperative image of the simulation surgery. XII: Postoperative image of the actual nephron-sparing surgery of Patient 1.

During the segmentation phase, the preoperative imaging (MRI or CTA) was segmented to create a 3D model of the tumor, kidney, and arterial vasculature in 3DSlicer version 4.11.20200930 as described in our earlier work (12).

Secondly, during the 3D printing phase, the casting molds for both the kidney and tumor were designed in computer-aided design

software (Autodesk Fusion 360 version 2.0.11405; Autodesk, Inc., Mill Valley, CA, USA). The casting mold of the kidney consisted of three parts: a top, bottom, and arterial inlay (Figure 6-2; ▼). The different parts were prepared for 3D printing with Cura 4.10.0 (Ultimaker, Utrecht, The Netherlands). The top and bottom for both the kidney (Figure 6-2; ✻) and tumor casting molds (Figure 6-2; ✻) were 3D printed with polylactic acid (PLA) with a dual extrusion printer (Ultimaker S5; Ultimaker, Utrecht, The Netherlands). The arterial inlay and hollow artery model were printed with high intensity polystyrene (HiPS; Formfutura, Nijmegen, The Netherlands) and FilaFlex TPU 60A (Recreus, Elda, Spain), respectively. The inlay for the arterial vasculature was used to ensure precise positioning and orientation within the phantom of the intraparenchymal arteries. For the tumor and kidney hydrogel, we used 7% water/weight ratio poly-vinyl alcohol (PVA; Mw 89,000-98,000, 99+% hydrolyzed; Sigma-Aldrich, St. Louis, MO, USA). Glass microspheres (0.5 grams per ml) were added to the hydrogel of the tumor to create contrast between the tumor and kidney tissue in the US imaging.

At the start of the hydrogel casting phase, the casting mold of the tumor was filled with the hydrogel and underwent one freeze/thaw cycle (Figure 6-2; ■). The tumor hydrogel was removed from the tumor casting mold and positioned in the bottom part of the casting mold of the kidney. Subsequently, the arterial inlay was positioned in the bottom part. The complete mold was filled with PVA hydrogel and received two freeze/thaw cycles. After these cycles, the tumor and kidney hydrogel phantom with the arterial inlay (Figure 6-2; ✚) were removed from the casting mold and placed in limonene overnight to dissolve the HiPS inlay (Figure 6-2; **X**). The different number of freeze/thaw cycles between the kidney and tumor allow for T2-weighted MRI contrast necessary for post-procedural analysis with MRI (10).

This approach resulted in a patient-specific phantom mimicking kidney and tumor tissue with arterial vasculature, surgically resectable and compatible with US and MRI.

6.3.2 Surgical procedure

We developed a life-size pediatric abdominal silicone phantom to simulate the abdominal cavity. The patient-specific hydrogel phantom was positioned inside the abdominal cavity of the phantom. At the start of the simulation procedure, the surgeon first inspected the preoperative imaging and the corresponding 3D model of the patient with augmented reality using a HoloLens 2 (Microsoft, Redmond, Washington, USA). The surgeon subsequently used intraoperative US to

locate the tumor and determine its margins. Finally, the surgeon resected the tumor.

6.3.3 Postprocedural analysis

After the simulation procedure, both the resected tumor and residual phantom renal tissue were analyzed with high-resolution MRI to determine the smallest surgical margin. Moreover, the MRI of the postoperative kidney phantom was segmented to delineate the kidney volume of the specimen. The expected remaining kidney volume of the patient was calculated, expressed as a percentage.

6.3.4 Quantitative Evaluation

After the surgical procedure, a self-developed questionnaire with 11 open, closed and agree/disagree questions was used to evaluate the simulation procedure. The agree/disagree questions used a 5-point Likert-scale indicating 1: strongly disagree; 2: disagree; 3: neutral; 4 agree; 5 strongly agree. The questionnaire compared the simulation procedure with the actual nephron-sparing procedure, objectified what the surgeon learned from the simulation and analyzed the additional benefit of the simulation procedures for preoperative planning and actual surgery.

6.4 RESULTS

Patient 1

A two-year-old boy with a WT-1 mutation was diagnosed with a renal tumor of the left kidney. He was previously treated for a stromal right-sided WT with a right-sided total nephrectomy, and known to have left-sided nephroblastomatosis for which he received monthly vincristine- actinomycin D (VA) over the course of one year. The patient presented with a new lesion seen on follow-up imaging seventeen months after end of chemotherapy. The lesion was situated within the nephroblastic tissue, near the hilar region in the lower pole of his remaining left kidney. The lesion measured 2.3x2.9x2.7 cm (9.4 ml). After six weeks of neo-adjuvant VA, an MRI was performed, not showing significant reduction in size (2.0x2.6x2.7 cm; 7.3 ml). To achieve further tumor reduction to facilitate NSS, chemotherapy was switched to two cycles of carboplatin and etoposide (CE). After CE treatment, the size of the tumor was sufficiently reduced (1.9x1.9x1.6 cm; 3 ml) and NSS was considered feasible.

A 3D model was created based on a CTA made after four weeks of VA. For the 3D model, it was decided to visualize both the tumor and

the nephroblastomatosis as one lesion as both would be resected en bloc. The lesion had a narrow relationship with a small arterial branch after the first bifurcation. Segmentation of the CTA took 76 minutes. The kidney had a volume of 85 ml. The 3D printing time of the casting molds of the kidney and tumor was nine hours and 43 minutes in total. 3D printing of the artery with inlay required five hours and 51 minutes. The complete production time was five days including one day for 3D printing, three days for the freeze/thaw cycles and one day for dissolving the HiPS inlay surrounding the artery.

The surgical team (two pediatric surgeons and one pediatric urologist) who planned to perform the actual NSS viewed the 3D model of the patient in augmented reality. The influence of the position of the tumor and the relationship with the arterial branch at the resection border was discussed. Together the resection border was determined using intraoperative US on the phantom. The tumor was resected in eight minutes. The phantom specimen with tumor, nephroblastic and kidney tissue measured 3.9x3.6x3.5 cm. The post-procedural MRI showed a complete removal of the tumor with the smallest clear margin measuring 0.13 cm. The volume of resected phantom kidney tissue was approximately 41 ml based on the segmentation, resulting in an expected volume of remaining renal parenchyma of 52%.

During the actual surgery, the resection border was determined with intraoperative US. The renal vessels were clamped, and the kidney was cooled with crushed ice. After ten minutes of cooling, the tumor and nephroblastic tissue were resected en bloc. The pyelum was opened cranial to the tumor and closed after resection of the tumor. After 52 minutes of ischemic time (including the period of cooling), the entire remaining renal tissue showed arterial flow.

The macroscopic tumor size was 2.5x3.2x1.4 cm. Pathology showed a stromal tumor surrounded by nephrogenic rest, with sinus invasion. The tumor was not enclosed by renal parenchyma due to the resection border with the pyelum. However, the tumor was considered completely resected. Lymph nodes showed no metastases. The tumor was staged as intermediate risk histology, stage II. The patient is currently receiving 27 weeks of VA, which will be followed by monthly VA doses for a treatment duration of one year.

Patient 2

An 18-month-old boy with no relevant past medical history presented in our hospital with both a WT and nephroblastomatosis of the right kidney and nephroblastomatosis of the left kidney. The initial tumor size was 2.3x2.1x4.0 cm (10 ml). Additionally, there was a lesion in the right adrenal gland, hemangioma in the liver, a cyst in the

pancreas and small pararectal nodular lesions. The patient was diagnosed with Beckwith-Wiedemann syndrome after genetic examination. After six weeks of chemotherapy (VA), the tumor had reduced in size (1.2x0.6x2.2 cm; 1 ml). To further reduce the tumor size and possibly allow conservative management, six more weeks of VA were given. Further reduction (0.9x0.5x1.5 cm; <1 ml) was achieved, however, the tumor was still present on follow-up MRI, therefore necessitating NSS. The remaining surrounding nephroblastomatosis was difficult to identify on preoperative MRI.

In the 3D model, the tumor and nephroblastomatosis were visualized as one lesion. The 3D model of the kidney had a volume of 56 ml. Segmentation of the MRI for the digital 3D model took 47 minutes. The combined 3D printing time of the casting molds of the kidney and tumor was 11 hours and 12 minutes. 3D printing of the artery required eight hours and six minutes. The production of the phantom was completed in roughly five days.

At the start of the simulation procedure, the tumor outline was marked with a small incision on the phantom guided by intraoperative US. After agreeing on the location of the resection margins, the lesion was resected. The phantom specimen measured 1.7x1.4x0.7 cm. The post-procedural MRI showed a complete removal of the tumor with the smallest clear margin measuring 0.15 cm. The volume of resected phantom tumor was approximately one ml, resulting in an expected volume of remaining kidney parenchyma of 98%.

The actual surgery was performed four days after the simulation. Determining the border of the tumor during surgery with intraoperative US proved to be difficult due to the adjacent nephroblastomatosis.

The macroscopic specimen was 2.0x1.1x0.6 cm. The completely removed centrally located lesion measured 1.0x0.7x0.5 cm and was partially encapsulated. The lesion contained cell free fibrous tissue with small vessels and macrophages, which was considered effect of therapy. The remaining tissue in the specimen was healthy kidney parenchyma and perilobar nephrogenic rest within the surgical resection border. Lymph nodes showed no metastases. The patient currently receives one year of postoperative monthly chemotherapy (VA).

Questionnaire

Questionnaires were completed after the NSS procedure by the performing surgeon. The results of the closed agree/disagree questions are shown in Table 6-1. Surgeons agreed that the resection performed on the phantom accurately matched in position and size with the resection during the procedure.

There was no clear difference in preference for preoperative planning either with the conventional augmented reality using a HoloLens 2 or with the phantom simulation procedure. The surgeons commented on the lack of veins and urinary collecting system (UCS) in the phantom as a notable flaw. The surgeons claimed that they would like to use phantom simulations for preoperative planning of NSS in the future, to improve the surgical procedure and reduce oncological risk.

Table 6-1 Results of the agree/disagree questions of the questionnaire. The agree/disagree questions used a 5-point Likert-scale indicating 1: strongly disagree; 2: disagree; 3: neutral; 4 agree; 5 strongly agree or Not Applicable (N/A, opinion of the surgeon). S1 = Surgeon 1, S2 = Surgeon 2. Open questions 2 to 7 are not included in the table. *UCS = Urine collection system

Question	**S1**	**S2**
1a. The size of the kidney of the phantom correlated accurately with the kidney of the patient.	5	5
1b. The size of the tumor of the phantom correlated accurately with the tumor of the patient.	5	4
1c. The location of the tumor of the phantom correlated accurately with the tumor of the patient.	5	3
1d. The shape of the arteries of the phantom correlated accurately with the arteries of the patient.	5	N/A
1e. The shape of the veins of the phantom correlated accurately with the arteries of the veins.	N/A	N/A
1f. The shape of the UCS* of the phantom correlated accurately with the UCS of the patient.	N/A	N/A
8. The phantom simulation contributed to		
8a. the preoperative plan for the removal of the tumor.	4	4
8b. the preoperative plan for the clamping of the vessel.	1	4
8c. understanding of the intraoperative ultrasound.	4	4
8d. shortening the time required for intraoperative ultrasound.	1	2
8e. shortening the time required for ischemia.	3	N/A
8f. shortening the duration of the operation.	3	4
9a. Analyzing the MRI of the tumor of the phantom helped me prepare for the upcoming NSS.	1	N/A
9b. The ultrasound of the phantom accurately matched with the intraoperative ultrasound.	5	2

Question	S1	S2
9c. Communication with the surgical team improved due to the additional time spend planning.	4	5
9d. Communication with the surgical team improved by pinpointing details on the phantom.	5	4
10. The preoperative planning with the HoloLens 2 helped me to get a good insight in:		
10a. the size and shape of the kidney.	3	4
10b. the localization and infiltration of the tumor.	5	4
10c. the localization and course of the arteries.	5	N/A
10d. the localization and course of the veins.	5	N/A
10e. the localization and course of the UCS.	3	N/A
10f. the relationship of the tumor and the arteries.	5	4
10g. the localization and depth of the required resection.	4	5
11. The preoperative planning with the phantom simulation helped me to get a good insight in:		
11a. the size and shape of the kidney.	5	4
11b. the localization and infiltration of the tumor.	4	2
11c. the localization and course of the arteries.	5	4
11d. the localization and course of the veins.	5	4
11e. the localization and course of the UCS.	N/A	4
11f. the relationship of the tumor and the arteries.	5	4
11g. the localization and depth of the required resection.	5	4

6.5 DISCUSSION

NSS for WT is a selective and difficult procedure with strict indications and even in experienced centers, 30% of tumors appear microscopically not to be completely removed (13). Extensive surgical planning and expertise is vital for safe resections. To improve our preoperative planning strategy and increase our experience with NSS, we used patient-specific hydrogel phantoms. In the two cases described, this technique helped to safely perform NSS whilst achieving clear margins and to preserve as much healthy renal parenchyma as possible. Our technique may also allow the use of NSS in patients typically regarded as ineligible for this procedure. By protocol, non-syndromic unilateral WT patients are not considered for NSS if tumor volume at diagnosis exceeds 300 ml (1) within the UMBRELLA SIOP-RTSG 2016 protocol. Even after a significant reduction in size due to neoadjuvant chemotherapy, the treatment protocol dictates a total nephrectomy (1).

However, with simulation surgery, we can more accurately determine the difficulties of the procedure and estimate the expected volume of remaining kidney parenchyma. This allows for a more substantiated assessment of possibility for NSS. In the future, this thorough assessment may allow for NSS to be performed more frequently, thereby reducing long-term treatment-related complications, without taking unnecessary oncological risks.

Visualizing the surgical plane and estimating the surgical approach was considered the most valuable result of this described technique. It was reported as a major advantage to locate the tumor intraoperatively based on a recollection from the simulation procedure. Moreover, remembering the surgical plane of the resection ensured a correct understanding of the surgical route. The ability to rely on preoperative planning emphasizes the importance of the accuracy of the phantom. Recently, the production and resulting accuracy of hydrogel phantoms for complex urological procedures has been described thoroughly (14). Tumor positioning was considered accurate with a mean positional alignment of -0.1 mm. In our study, for patient 2, the tumor was located more ventrally during the procedure in comparison to the phantom which may have been caused by movement of the tumor during the hydrogel casting. This did not interfere with the surgical procedure, mainly because of the relatively easy procedure in this case. For the arteries, the mean positional alignment deviation in the study of Melnyk et al. was 4.93 mm with a maximum of 15.6 mm (14). To decrease this error, we 3D printed the arteries within a dissolvable HiPS inlay using a dual extrusion printer. This ensured the level of positional and orientation accuracy required for nephron-sparing surgery. Both surgical teams observed a high accuracy of the intraparenchymal arteries of the phantom in comparison with intraoperative findings. Unfortunately, this accuracy was only assessed qualitatively in the two cases. Further quantitative comparison of the phantom and MRI segmentations is required to determine the accuracy of our phantom production technique.

This feasibility study has limitations. Firstly, although the described two cases allow for a statement of general feasibility of phantom simulations, these data are not robust enough to be generalizable and should be studied further in a larger prospective cohort. Secondly, the technique requires extensive technical knowledge and dedicated technicians working with the surgical team. This may be more difficult to realize in general care. Thirdly, we did not include veins, UCS and blood flow in our phantoms which reduces the fidelity of these particular models. However, in combination with augmented reality the surgeons gain insight into all important structures of the kidney in

relation to the tumor. In future phantom models we aim to include the veins and the UCS. Finally, the currently required five days of production time may be too long to be able to perform simulation surgery between the preoperative MRI and the actual surgical procedure in certain cases.

Patient-specific phantoms may allow for more applications. Firstly, the phantoms may allow to determine the possibility of brachytherapy for patients requiring NSS which is a technique only performed in highly selected cases (15). The feasibility is determined by an experienced multidisciplinary team and depends on multiple anatomical factors such as the location and size of the tumor and the shape of the expected resection. With hydrogel phantoms, the size of the required brachytherapy applicator and feasibility of the technique can be planned before the actual procedure. Moreover, closure of the renal capsule around the applicator can be simulated. Secondly, simulation phantoms can offer insight into the feasibility of laparoscopic NSS (16). With laparoscopic NSS, tumor spillage and consequently upstaging of disease is generally considered a particular risk. For this reason, the UMBRELLA SIOP-RTSG 2016 protocol contraindicates the use of laparoscopy for NSS. The development of a laparoscopic patient-specific NSS simulator may possibly allow for a laparoscopic approach in highly selective cases. Thirdly, patient-specific phantoms may be used to train pediatric surgeons focusing on pediatric oncologic surgery. Finally, this proposed technique can strengthen the surgical indication for NSS in patients currently considered ineligible.

In the future, this work will be continued in a larger prospective cohort. Moreover, we recommend to perform a direct comparison of the two preoperative planning techniques, AR and simulation surgery, to distinguish the additional value of AR in our surgical planning workflow.

6.6 CONCLUSION

Preoperative simulation with patient-specific hydrogel phantoms is a feasible and useful technique for the preparation of NSS in WT patients. The simulation surgery helped perform NSS more safely. In the future, this technique may further help to achieve negative surgical margins in NSS and may also allow the use of NSS in patients typically regarded as ineligible.

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Chapter 7 Holographic navigation for pediatric kidney tumor surgery, a feasibility study

This chapter is based on

Fitski, M., Van der Steeg, A. F. & Wijnen, M. H. (KWF *Call 2022-3 Development & Implementation Project 14714*). Holographic navigation for pediatric kidney tumor surgery, a feasibility study.

7.1 SCIENTIFIC ABSTRACT

Problem description: In the Netherlands, roughly 30 children are diagnosed with renal cancer each year and therewith it is one of the most occurring solid tumors in childhood. 6 to 7 of these patients require nephron-sparing surgery (NSS), i.e., the surgical removal of only the tumor while leaving the kidney in situ. It is most frequently performed in patients having bilateral disease or an underlying congenital syndrome. Unfortunately, current figures report positive surgical margins of the resection in NSS between 15.7 % and 31 % (1,2). Patients with this complication require additional chemotherapy, possibly radiotherapy and have a lowered prognosis.

Research solution: To help us improve nephron-sparing surgery, we have developed holographic surgical software. This technique uses HoloLens glasses to depict holograms of the kidney of the patient based on preoperative imaging. These holograms are then projected onto the real kidney of the patient during surgery. With this technique we visualize important anatomical relationships which are normally invisible for the surgeon. We expect this technique will help the surgeon more accurately remove the tumor from the kidney. This work focusses on implementation of holography during nephron-sparing surgery.

Aim: Our aim is to perform a feasibility study to implement this new surgical tool. With this implementation, we aim to improve our surgical accuracy. We have defined two objectives to reach that goal.

The first objective is to test the HoloLens technique inside patients undergoing a total nephrectomy inside the operating room. We study how the software positions the holograms in a real surgical setting on a real kidney. This allows us to quantify the influence of the deformation of the organ on the visualization with the HoloLens. Additionally, surgeons get comfortable with performing surgery with the HoloLens without additional risks for our patients.

Secondly, we aim to perform a pilot implementation study to implement the HoloLens technique during NSS.

With this proposal, we hope to eventually increase the surgical accuracy of nephron-sparing surgery. We assess the clinical accuracy, workload and feasibility of this holographic software and hope to increase the number of patients eligible for nephron-sparing surgery. If we improve our procedure and broaden the indication, an expected 10 to 12 patients per year might be eligible for NSS.

Plan of investigation: The first workpackage is designed as a clinical, mono-center, observational study in which we use the HoloLens during surgery. It does not change surgical approach and is not

subjected to the WMO. For this study, we include all patients eligible for a total nephrectomy older than 6 months and younger than 18 years of age over the course of a year, which is roughly 20 patients.

The second workpackage is composed as a clinical, mono-center, investigator-initiated, interventional, implementation, pilot study and is subjected to the WMO. We aim to include all children eligible for nephron-sparing surgery. Again, only patients older than 6 months and younger than 18 years of age are included. We expect to include 5 resections in one year.

Expected outcome: The goal is to improve nephron-sparing surgery with the use of holograms. We expect to improve surgical accuracy and therewith aim to reduce the amount of positive surgical margins. Through improving our surgical accuracy, we might also be able to increase the indication for NSS. This might make NSS more available to our WT patients now requiring a total nephrectomy. Afterwards, we might also consider this hologram technique for other oncologic pediatric surgical procedures in which holograms might help such as surgery for neuroblastoma, sarcoma and liver tumors.

7.2 RELEVANCE TO KWF MAIN GOALS

Through the implementation of holographic surgical navigation technology, we aim to **improve surgical treatment** for patients with Wilms' tumors receiving nephron-sparing surgery. The goal is to reduce positive surgical margins which reduces additionally required chemotherapy and radiotherapy. This improves the prognosis, improves **the overall quality of life** and reduces long-term treatment-related complications such as renal failure later in life for these young patients.

7.3 PROJECT PROPOSAL

Problem and research direction or solution

The most occurring tumor of the kidney in childhood is Wilms' tumor (WT) with an annual incidence of 0.7 in 100.000 children younger than 15 years. Response to therapy is high, with overall survival rates of over 90% (3,4). Surgical treatment consists of a total nephrectomy (TN), complete removal of the kidney and tumor, or nephron-sparing surgery (NSS) in which the tumor is removed from the kidney. The goal of NSS is to preserve functional renal tissue, whilst achieving a complete tumor resection (5). It is considered for bilateral patients and patients with a congenital syndrome (6 to 7 patients each year). Unfortunately, between 15.7% and 31% of the tumors are incompletely removed, a so-called

positive surgical margin (1,2). For these patients, the treatment protocol advocates additional chemotherapy and possibly radiotherapy.

Unilateral WT patients are predominantly treated with a total nephrectomy due to large tumor size, localization and the increased difficulty and involved risks of NSS. However, the expected improved renal function and reduced risk of end-stage renal failure is a major long-term advantage of NSS. This necessitates further insights to perform NSS more frequently in unilateral patients, whilst also reducing the possible risks. It is expected that between 9% and 24% of non-syndromic unilateral WT patients might be eligible for NSS (6,7). Thus, if we improve our procedure and broaden the indication, 10 to 12 patients might be treated with NSS per year.

To reduce positive surgical margins, a detailed understanding of the anatomical relationships of each specific patient is vital. Yet this is difficult to understand based on conventional 2D imaging such as MRI. Novel surgical visualization techniques can help to gain an improved understanding of the 3D anatomical relationships of the crucial structures of the kidney such as vasculature and tumor localization and infiltration. These anatomical relationships can be shown in 3D with a HoloLens. A HoloLens is a display worn by the surgeon which depicts holograms of the patient anatomy. An example is given in Figure 7-1.

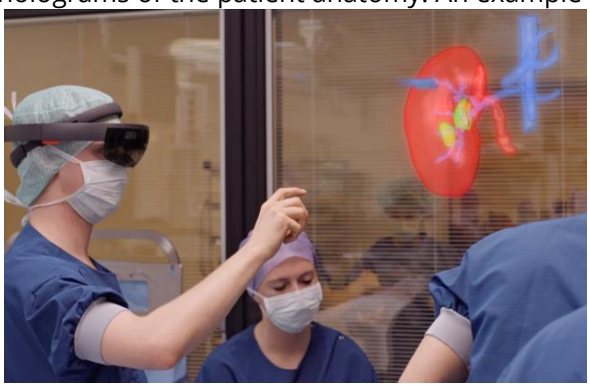

Figure 7-1 Example of our team using augmented reality with a HoloLens to prepare for nephron-sparing surgery. Through the HoloLens, the user looks at the patient-specific hologram to understand the anatomical relationships between the vasculature and the two centrally located tumors (green).

We expect that the implementation of holography during surgery helps us improve our anatomical understanding and our surgical performance. This technique may help us to prevent these positive surgical margins and thus improve the patient outcome of nephron-sparing surgery.

7.3.1 Aim

The aim of this project is to perform a feasibility study to improve nephron-sparing surgery with the implementation of holograms during surgery. Using holograms, we can see the depth of the tumor during surgery, which is otherwise invisible. The goal is to improve intraoperative surgical understanding and decrease the surgical difficulty of nephron-sparing surgery.

For this project, we have defined 2 workpackages with separate research objectives.

1. Workpackage 1: Operating with the HoloLens

The objective is to determine the difference between the rigid hologram and the deformable kidney. Moreover, we need to learn how to operate while wearing the HoloLens in a real surgical environment. Therefore, we perform a patient study with patients undergoing a total nephrectomy. During a total nephrectomy, we can safely use the HoloLens and learn to accurately position the holograms inside the patient.

2. Workpackage 2: Holography implementation pilot during NSS

If we can confirm an accurate holographic overlay inside patients, confirm the surgical feasibility and if surgeons feel comfortable with the technique, the objective is to implement this technique during NSS in a pilot patient study.

In the future, we hope to reduce the amount of positive surgical margins and to increase the number of patients eligible for nephron-sparing surgery. Moreover, if successful, we aim to implement this holographic technique for other patients such as neuroblastoma - and liver tumor patients.

7.4 BACKGROUND

Summary of literature

3D modelling for preoperative planning

To get a better understanding of the patient-specific anatomical relationships, visualization techniques are required which help the surgeon interpret medical imaging. 3D anatomical modelling is such a technique which is increasingly used during the preoperative planning of NSS. A clear 3D visualization of the tumor infiltration and the vasculature inside the kidney helps us better understand anatomical relationships, in comparison to the regular 2D perspective of classical imaging data from CT or MRI (8,9). 3D models are computed from this imaging data. These anatomical models can be shown with different techniques such as 3D printing and augmented reality (AR). AR allows

the user to see holographic 3D models in a real-world environment using a HoloLens. Both techniques have been implemented for preoperative use in our center in the recent years.

Intraoperative visualization in children

Intraoperative visualization techniques implement preoperatively computed 3D models during the actual surgical procedure to guide surgeons. Multiple small studies have shown the advantage of intraoperative use of 3D models for renal laparoscopic surgery (10–15). The 3D models can be rigidly projected on to the 2D monitor of the laparoscopic camera. In this type of intraoperative visualization, the projection depicts the underlying vasculature and localization of the tumor necessary to guide the surgeon towards a safe resection. Understanding these anatomical relationships and their position is crucial for a complete safe removal of the tumor during NSS (16).

In contrast to adult surgery, pediatric nephron-sparing surgery requires a vastly different approach. We perform NSS in an open abdominal approach and not laparoscopically nor through an open lumbar incision common in adults. Moreover, a positive surgical margin in pediatric surgery has a bigger impact on the treatment and survival of the child opposed to adult surgery (17). Therefore, visualization techniques used in adults are not directly translatable to pediatric oncologic surgery. Within this pediatric context, a sense of depth to understand the infiltration of the tumor in the kidney tissue is more important. This requires intraoperative 3D visualization instead of 2D on a monitor. For this 3D visualization, AR with a HoloLens can be used to navigate in the open real-world surgical view. This intraoperative holographic visualization technique has been described for orthopedic, maxillofacial and neurological surgery (18–20).

The use of intraoperative holograms for open abdominal surgery has only been reported on a case-by-case basis (21). Unfortunately, the matching accuracy of the proposed technique by Tang et al. was not qualitatively measured. We propose to combine the techniques used in adults for laparoscopic NSS and by Tang et al. (2017) for hemihepatectomy. This will allow for intraoperative visual guidance, specifically tailored to our pediatric surgical needs during open NSS. We expect that intraoperative holographic visualization during NSS can help us improve our intraoperative understanding of the 3D patient-specific anatomical relationships. Therewith we reduce the amount of positive surgical margins in Wilms' tumor patients.

Preliminary results of own research

Preoperative planning

In an earlier retrospective study, researchers of the Princess Máxima Center and the Radboudumc 3DLab found an improved understanding of the patient-specific anatomy of patients with Wilms' tumors when using 3D visualization techniques. The patient-specific 3D models were compared to traditional imaging techniques such as CT and MRI (9). In this study, patient-specific 3D models were reconstructed based on the preoperative imaging of 20 patients. Both augmented reality (AR) and 3D printed models resulted in an improved preoperative understanding of the patient-specific anatomy in comparison to conventional imaging data. The authors reported limitations in image quality, segmentation techniques, duration, and costs of the visualization techniques.

We overcame the limitations from this earlier study and improved the use of patient-specific 3D anatomical models for patients with WT resulting in a "3D visualization workflow" (22). This led to an advanced, fast and reliable technique to preoperatively visualize patient-specific anatomical 3D models. The workflow can be performed within a day after the preoperative MRI, allowing the surgeons to prepare well in advance for the surgical procedure. Figure 7-2 shows the 3D model of one patient as visualized through three different techniques.

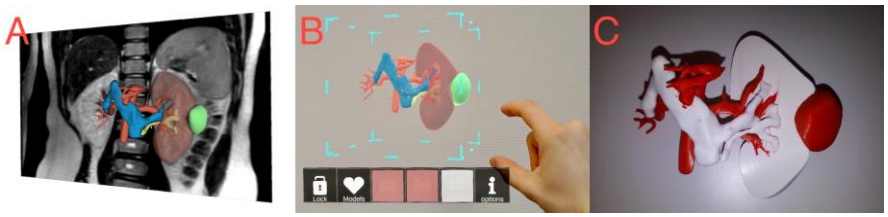

Figure 7-2 Visualization of patient-specific anatomical 3D models for the preoperative planning of nephron-sparing surgery in Wilms' tumor patients. A: Virtual rendering in the open-source software package 3D Slicer. B: Photo made by cameras of the HoloLens showing the self-built software. C: a 3D printed physical model. Adapted from Fitski et al. (2020).

The now available high-fidelity 3D visualizations also allowed for more insightful surgical planning approaches. Firstly, we adapted a virtual resection tool in 3DSlicer to perform NSS digitally and preoperatively determine the resulting amount of remaining renal parenchyma (23). This technique is shown in Figure 7-3 I and II. In a

retrospective analysis, the volume of the remaining renal parenchyma of 9 cases of NSS was compared to the resulting volumes from the virtual resection tool. With a median volume fraction of 0.94 (ranging from 0 to 1), the tool was considered accurate and appropriate to be used for NSS in pediatric patients. Currently we use the technique to communicate the planned resection with the surgical team. Secondly, the 3D models can be used to create patient-specific hydrogel phantoms for simulation surgery and can be imaged using conventional techniques (ultrasound and MRI) (24). This technique is shown in Figure 7-3 III and IV. We have created patient-specific phantoms and performed simulation surgery prior to two cases of NSS. Although the development of these phantoms takes an average of 5 days, the simulation surgery was considered very useful during preoperative planning and allowed the surgeons to get a sense of tumor localization and infiltration. Moreover, with postoperative imaging of the specimen of the phantom, we were able to visualize the size of the surgical margin to confirm the safety of the planned surgical approach.

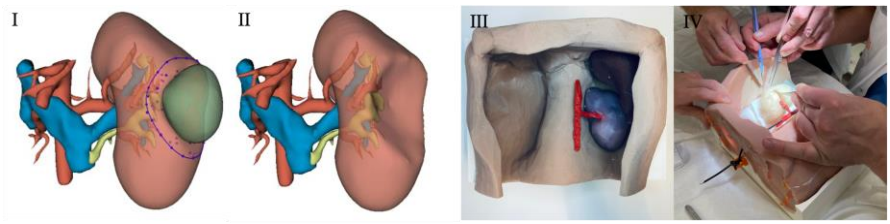

Figure 7-3 Two different advanced preoperative planning approaches; I and II: Virtual resection performed on a patient-specific 3D model (adapted from Zee et al.). III and IV: Simulation surgery performed on a patient specific hydrogel phantom (adapted from Fitski et al.).

Intraoperative visualization

After development of the preoperative visualization software and preoperative planning approaches, holographic software development has focused on the intraoperative use of holograms for surgical visualization (19).

The 3DLab of the Radboudumc developed a technique which makes use of positional markers recognized by the HoloLens. These positional markers allow the HoloLens to position the hologram at the exact location in the operation field in relationship to the patient, a process called matching. The matching process is independent of the tissue to be visualized. As such, we used this technique to visualize a

chest wall soft-tissue sarcoma for which we also thoroughly described the technique (25).

The department of pediatric surgery at the Princess Máxima Center has implemented this matching software for pediatric renal cancer surgery in a technical validation. The aim of this study was to measure the technical matching accuracy of the software and understand how this holographic visualization software influences the surgeons.

For this technical validation we constructed a pediatric abdominal model containing a liver and spleen made of silicon. The kidney phantom was 3D printed. The different patient-specific kidney phantom was interchangeable within the abdominal silicon model.

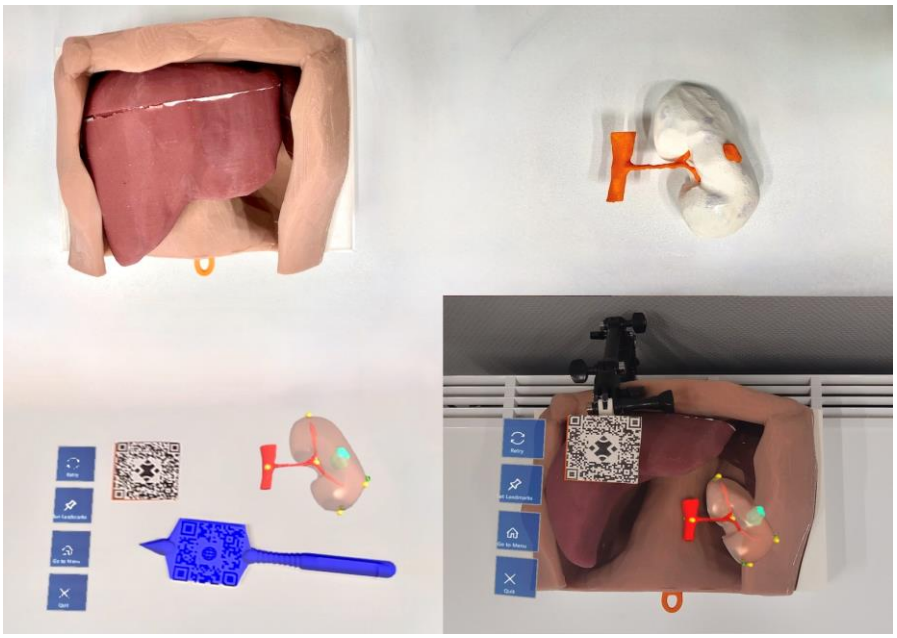

Figure 7-4 Overview of the phantom with the holographic overlay. We have developed an abdomen model of a three-year-old child (top left). The 3D printed kidney phantom corresponds to the anatomy of the patient (top right). The matching hologram (bottom left) is shown to the surgeon and is used as an overlay on the kidney phantom inside the abdomen (bottom right).

The software uses an algorithm to match predefined digital points to points on the phantom. These points are pinpointed by the surgeon with a surgical tool. The algorithm then positions the hologram based on the pinpointed points on the expected position, the kidney

phantom. The difference between the expected position and the actual position of the hologram is the matching accuracy error. The preliminary results of the technical validation show a matching accuracy within the clinically determined error margin of 5 mm. The matching algorithm had an error of the holograms of 3.16 ± 1.82 mm. Moreover, we asked five pediatric surgeons specialized in oncology to use the holographic navigation software. The models, holograms and resulting overlay are shown in Figure 7-4 and the view of the surgeon can be seen in this video. After positioning the hologram onto the simulated surgical site, the surgeons were asked to fill in a questionnaire based on the validated NASA-TLX workload assessment and a self-developed questionnaire specifically developed to evaluate our approach. The results of the questionnaires revealed an expected low physical and temporal workload for the surgeon and validated the user-friendliness of the system. There was no significant difference in expected value of this approach for the different pathologic presentations mimicked by the phantoms. The technical validation confirmed that the algorithm works as technically expected, within the clinically determined error margin.

Currently we are performing a surgical phantom simulation study. This clinical phantom validation study aims to determine the feasibility of performing surgery with the HoloLens technique and validate the improved surgical accuracy. In this study, the surgeons are asked to either use US or the HoloLens for surgical visualization during the simulation of nephron-sparing surgery with patient-specific hydrogel phantoms.

With the US, the surgeon determines the tumor location, infiltration depth and the relationship to the vasculature.

With the HoloLens, the software then positions the hologram onto the phantom. The surgeon determines to the tumor location, infiltration depth and the relationship to the vasculature based on the hologram. The surgeon measures the difference of the border of tumor in the hologram with the border of the actual tumor. The surgeon aims for an accuracy of 2 mm. If the accuracy of the position is worse than 5 mm, the position is considered inaccurate and the surgeon needs to reposition. If the position is considered accurate (<5 mm) but the surgeon is not satisfied with the position of the hologram, the surgeon can reposition one time.

After performing the surgical visualization, the surgeon has 30 minutes to safely resect the tumor. The results of the phantom study will be analyzed in two ways. First, after each session, we use a questionnaire to evaluate the experience of the surgeon and evaluate the feasibility of the technique. In this questionnaire, we use the NASA-TLX Workload tool to assess the workload experienced by the surgeon.

Additionally, we ask questions which are specific to our procedure. These questions, based on a Likert scale, allow for a more specific assessment on how the surgeons experience the simulation. Moreover, we study how the surgeons expect the holographic software helps them improve NSS and how it relates to the conventional ultrasound technique.

Secondly, we use postprocedural imaging. The resected specimens are scanned with MRI to measure the width of the rim of normal kidney tissue. This allows us to determine the surgical margin.

This clinical phantom validation study is currently performed in our center and the results are expected to be published in 2022. The phantom study is used in preparation for workpackage 1.

7.5 PLAN OF INVESTIGATION

Our objective is to perform a feasibility study with the goal to implement a new surgical tool. Herewith, we aim to reduce the number of positive surgical margins during NSS and to improve our intraoperative understanding of the anatomy of the patient.

During workpackage 1 “Operating with the HoloLens” we aim to confirm the overlay accuracy of our holograms on the deformable kidney inside the patient. Also, we learn how to operate while wearing the HoloLens in an actual surgical setting. We start with patients undergoing a total nephrectomy, taking no unnecessary risks.

If we successfully confirm the surgical feasibility, confirm an accurate holographic overlay inside patients and if surgeons are comfortable with the technique, we continue with workpackage 2 “Holography implementation pilot during NSS”. The objective is to implement holographic guided surgery during NSS in a pilot study. In this study, the surgeons use the holograms in combination with the conventional ultrasound.

Gantt chart

	Task	2023				2024			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Workpackage 1	Milestone 1								
	Milestone 2								
	Milestone 3								
Workpackage 2	Milestone 1.5								
	Milestone 4								
	Milestone 5								

This Gantt chart illustrates the time path of the three different workpackages over the course of 2 years (2023, 2024), subdivided into quarters (Q). The different milestones are explained in the detailed description of the workpackages.

7.6 WORKPACKAGE 1: OPERATING WITH THE HOLOLENS

Short description

To confirm the accuracy and to learn how to operate with the HoloLens, we test the technique in patients in a real surgical setting during a total nephrectomy.

Objective

The objective of workpackage 1 is to confirm the overlay accuracy of our holograms in a real surgical setting and to learn how to operate while wearing the HoloLens. We start with patients undergoing a total nephrectomy, taking no unnecessary risks.

Description of work

In the clinical surgical simulation study, we aim to validate the surgical improvement with the HoloLens technique we have practiced first in a phantom study. This phantom study allows us to overcome the expected learning curve without risks. However, the environment during surgery inside the operating room is different from the phantom environment in multiple ways including additional discomfort while wearing the HoloLens, additional difficulty to pinpoint the required points and, most importantly, a more deformable kidney.

The real-world differences of the deformable organ of the patient need to be studied as they can influence the accuracy of the HoloLens. Only then can we progress towards the implementation of the technique during nephron-sparing surgery. Moreover, in the real clinical workflow, we only have a couple of days between the preoperative imaging and surgery. We need to ensure that the preparation of the technique is feasible and consistent within the clinical workflow.

These differences need to be studied without taking risks for our patients. This is important for further implementation of the technique during nephron-sparing surgery. Therefore, we test the technique by using the HoloLens during a total nephrectomy. A total nephrectomy is the complete removal of the kidney with the tumor and takes several hours. The actual removal of the kidney is not influenced by the HoloLens and the hologram. This way we clinically test the HoloLens without additional risks for our patients.

For this study, approval of the Medical Ethics Assessment Committee (METC) is required. This necessitates an Investigational Medical Device Dossier (IMDD) for the software which is further explained under the section Ethical Considerations. We are currently working on the IMDD. Finishing the IMDD and obtaining METC approval is considered milestone 1.

The surgeons performing nephron-sparing surgery need to get comfortable with operating with the HoloLens. Before performing the technique intraoperatively, every surgeon participating in this study is asked to use the holographic navigation software on multiple different phantoms. In these practice rounds, the surgeons are familiarized with the technique without increasing the length of the actual procedure. After each phantom round, the surgeon is asked to fill in the NASA TLX questionnaire to verify the decrease of workload per round. The surgeon can only perform the technique intraoperatively if the surgeon is comfortable with the technique on phantoms based on this questionnaire. After every surgeon has successfully finished these practice rounds, milestone 2 is completed. Milestone 1 and 2 will be worked on simultaneously. After surgery we the comfort levels are determined using a 10-point rating scale with a questionnaire. With a self-developed questionnaire, the surgeon is asked to score the observed accuracy of the overlay of the hologram, and we study the feasibility of this approach in a surgical setting.

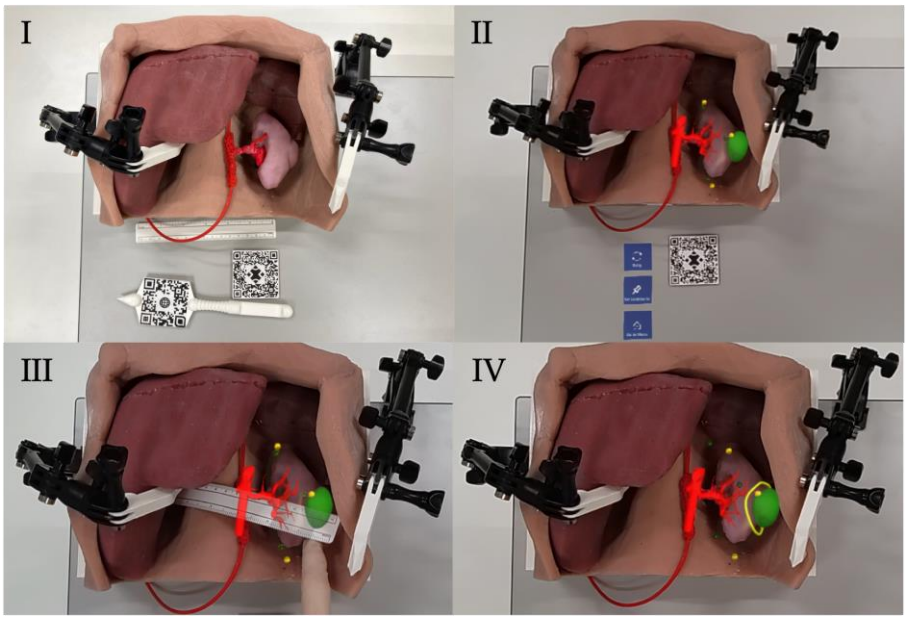

Figure 7-5 The protocol for measurement of the accuracy of the rigid hologram on a deformable kidney of the patient shown in a phantom; I: overview of the surgical field, the surgeon marks the tumor border with a felt-tip pen; II: the hologram is matched onto the phantom kidney using anatomical landmarks (yellow dots); III: the difference between the holographic and real tumor border is measured at four points with a sterile ruler; IV: the tumor resection border (yellow circle) is shown in the hologram for additional visualization.

To determine the clinical accuracy of the projected hologram, we need to understand the difference in position and size of the rigid hologram on the deformable kidney. The measurement used is shown on a kidney phantom in Figure 7-5. First, the surgeon measures the size of the kidney and tumor of the patient in the transversal and caudal direction. Then, the surgeon marks the tumor border onto the kidney of the patient with a sterile felt-tip pen (Figure 7-5 I). The hologram is subsequently matched on the kidney. After inspection of the complete hologram, the surgeon projects only the tumor on the kidney of the patient (Figure 7-5 II). The difference between the holographic and real tumor border is measured at four points with a sterile ruler (Figure 7-5 III). Furthermore, a picture is taken to measure the difference postoperatively. The biggest difference between both borders should be no more than 3 mm. If the difference is larger, the surgeon may reposition the hologram one time. The surgeon can project the digitally

prepared resection border onto the kidney for additional visualization (Figure 7-5 IV). The additional use of the HoloLens by the surgeon is allowed to prolong the nephrectomy procedure by a maximum of 10 minutes.

In addition to using the HoloLens during surgery, we ensure consistent preparation of the technique within the clinical timeframe.

This is a clinical, mono-center observational study in which we use of the holographic software in a real surgical environment inside the patient. The study is expected to take one year, ending after the inclusion of ± 20 patients. We expect that this number of patients is sufficient for the surgeons to overcome the expected learning curve of the technique.

Workpackage 1 needs to be completed before moving further towards implementation of this technique during nephron-sparing surgery in workpackage To finish workpackage 1, we have defined the following endpoints:

1. The overlay of the hologram needs to have an average accuracy of less than 2 mm inside the patient.
2. The subjective comfort levels of the surgeons as reported in the questionnaire need to be higher than an 8 based on a 10-point rating scale. We expect the comfort level to increase per procedure.
3. The surgeon needs to confirm the observed accuracy of the overlay of the hologram in the questionnaire. Based on a subjective 10-point rating scale, the average observed accuracy of the overlay of the hologram should be higher than an 8.
4. We need to be able to consistently prepare the hologram within clinical time constraints i.e. in the time between preoperative imaging and actual surgery. We define this by successfully preparing 10 consecutive patients.
5. Finally, we need to be able to position the hologram consistently and accurately on the deformable kidney. This is defined as being able to position the holograms with a positional error less than 2 mm and within 10 minutes consistently in 5 patients. This is considered milestone 3.

Study population

Patients with a renal tumor not eligible for nephron-sparing surgery are asked to participate in this part of the study. Verbal and written information about the study will be given to the parents/legal guardian by the surgical department or the research team. In- and

exclusion criteria are checked per patient by the surgical team or PhD-student to make sure the patient is eligible for the study.

To be eligible to participate in this study, a subject must meet the following criteria:

- Age between 6 months and 18 years
- Radiologically proven renal tumor
- Planned total nephrectomy
- Written consent signed according to local law and regulations

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Contraindications for total nephrectomy
- Unsuccessful preoperative MRI as determined by the Radiologist / PhD-student
- Indicated against inclusion by the surgeon

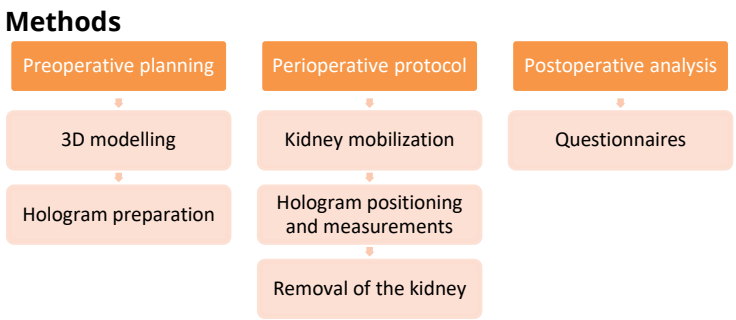

Figure 7-6 Overview of the three different periods for Workpackage 1. The three periods include: preoperative planning, perioperative protocol and postoperative analysis.

As shown in Figure 7-6, the protocol is divided into three periods: preoperative planning, perioperative protocol and the postoperative analysis.

Step 1: Preoperative planning

Before the start of the study, the patient and his or her parents / legal guardian are asked to participate and sign the patient information form. It is important to recognize that the patient is not subjected to anything different than the normal surgical procedure.

After inclusion, the 3D model of the patient is computed based on the standard preoperative imaging using the Mimics Innovation Suite (Materialise, Leuven, Belgium). This is CE-certified image analysis

software used for medical applications. Subsequently, the holographic matching software is prepared by defining multiple different anatomical landmarks in collaboration with the performing surgeon. Timewise, the software preparation needs to be performed between the preoperative MRI and the day of surgery.

Step 2: Perioperative protocol

The total nephrectomy starts with the regular surgical protocol, freeing the kidney with the tumor from the surrounding tissue. The surgeon marks the tumor border based on visual inspection of the kidney and tumor with a felt-tip pen. Then, the holographic overlay is started by using a surgical tool to pinpoint the digitally predefined anatomical landmarks on the kidney. The HoloLens recognizes these pinpointed positions, and this allows the HoloLens to position the hologram inside the patient. The surgeon observes the resulting holographic visualization carefully. The tumor border is holographically positioned on the kidney. The surgeon measures the difference in position of the tumor border of the hologram with the tumor border marked on the kidney as explained earlier. Subsequently, the surgeon continues with the conventional surgical procedure and removes the kidney from the patient.

Step 3: Postoperative analysis

Postoperatively, we ask the surgeon to fill in questionnaires. These are the NASA TLX questionnaire and a self-developed questionnaire to qualitatively assess the feasibility, comfort level of the surgeon, the user-friendliness, and the observed clinical accuracy of the technique.

Statistics

The results will be a description of the comfort of the surgeon as determined with a subjective 10-point scale. Additionally, we use 10-point scales to describe the user-friendliness of the holographic technology and a description of the feasibility for further use of the HoloLens during nephron-sparing surgery. The measurement of the position of the hologram is described as an average accuracy per patient and overall accuracy.

Ethical considerations

Regulation statement

This workpackage will be conducted according to the principles of the Declaration of Helsinki (3rd edition, 2015) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The

described study in this workpackage is considered a medical device study.

The self-developed positioning software does not intervene with the intended use of the HoloLens. The software is a functionality to help de surgeon position the hologram and the position can be adjusted at any time. This technique is already used for different surgical applications. This self-developed software with no CE-certification falls under the Medical Device Regulation, article 82.

The IMDD is drawn up in collaboration with the Information, Data and Technology Healthcare department (IDT) of our center. This IMDD contains all documentation regarding the safety, performance, and quality of the software acting as a summary of the technical documentation. The dossier ensures a consistent quality of the software. Furthermore, instructions of use are written with IDT. Both the IMDD and instructions of use will be sent to the METC.

Recruitment and consent

Patients will be recruited by the surgical team. Verbal and written information about the study (patient information letter) will be given to the parents/legal guardian after which they are given a minimum of three days to consider their decision. Written informed consent is asked before inclusion.

Benefits and risks assessment, group relatedness

In this study, we propose to use holograms to guide us during a total nephrectomy. During this procedure, the kidney is completely removed. The addition of holograms during surgery allows us to visualize this anatomy of the kidney and tumor in 3D.

In this study, we follow the standard surgical protocol for total nephrectomy. The addition of holograms is considered safe and does not interfere with the normal procedure. The holograms are only visible through the glasses of the HoloLens worn by the surgeon. They do not harm the patient. Our surgeons measure the accuracy of the position of the hologram. This positioning of the hologram and measurements may only take a maximum of 10 minutes. Also, the surgeons are accustomed to wearing the HoloLens after the phantom practice rounds. Therefore, we do not expect complications for our patients caused by the additional technique.

Compensation for injury

The sponsor/investigator 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.

7.7 WORKPACKAGE 2: HOLOGRAPHY IMPLEMENTATION PILOT DURING NSS

Short description

A pilot implementation study on the use of holographic navigation during nephron-sparing surgery.

Objective

If we have successfully confirmed the surgical feasibility, have confirmed an accurate holographic overlay inside patients and if surgeons are comfortable with the technique, we continue with the objective to implement holographic surgery during nephron-sparing surgery in Wilms' tumor patients.

Description of work

In workpackage 1 we used the HoloLens inside the operating room to learn how the position of the hologram matched with the kidney of the patient and we got comfortable with performing surgery with the technique without any additional risk for our patients. If all objectives of workpackage 1 are met, the next objective is to implement holographic surgery during nephron-sparing surgery in a pilot study.

We aim to further understand how surgeons perceive this holographic software as additional tool during surgery and how this guides our pediatric surgeons specifically during NSS. This will help us with our goal to improve our surgical accuracy in nephron-sparing surgery and to make NSS more accessible for WT patients.

In workpackage 2, we aim to implement the holographic technique during nephron-sparing surgery in patients with Wilms' tumors. We describe the clinical accuracy, surgical workload and usefulness of the technique through questionnaires. We use holography during surgery in a clinical, mono-center, investigator-initiated, interventional, implementation pilot study. This study is subject to the Medical Research Involving Human Subjects Act (WMO). All patients are included in the Princess Máxima Center for Pediatric Oncology. The duration of this pilot study is expected to be one year with an aim to include 5 nephron-sparing resections.

We have defined two milestones for this workpackage. Milestone 4 is the first successful application of intraoperative holography during NSS. Milestone 5 is reached after the successful implementation of NSS in five resections, at the end of clinical period of

the pilot study. A resection of the tumor of the fifth patient is also the endpoint of this workpackage.

Approval of the METC is required for this workpackage. We aim to obtain this approval during workpackage 1, simultaneously with milestone 1.

Figure 7-7 shows a flowchart of the design of this interventional implementation pilot study. After inclusion and successful preparation of the holographic navigation software, the patient is subjected to the standard nephron-sparing surgery protocol with additional use of the software. The patient received the standard treatment protocol in accordance with the SIOP-RTSG Umbrella treatment plan.

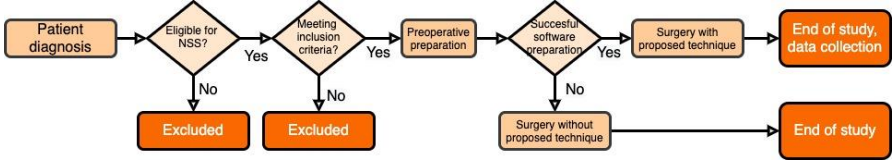

Figure 7-7 Flowchart of the design of the interventional implementation study: Intraoperative implementation during NSS.

Study population

Patients with a renal tumor eligible for nephron-sparing surgery are asked to participate in this study. Verbal and written information about the study will be given to the parents/legal guardian by the surgical department or the research team. In- and exclusion criteria are checked per patient by the surgical team or the PhD-student to make sure the patient is eligible for the study.

To be eligible to participate in this study, a subject must meet the following criteria:

- Age between 6 months and 18 years
- Radiologically proven renal tumor
- Planned nephron-sparing procedure within 30 days
- Written consent signed according to local law and regulations

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Unsuccessful preoperative MRI as determined by the Radiologist / PhD-student
- Indicated against inclusion by the surgeon

Methods

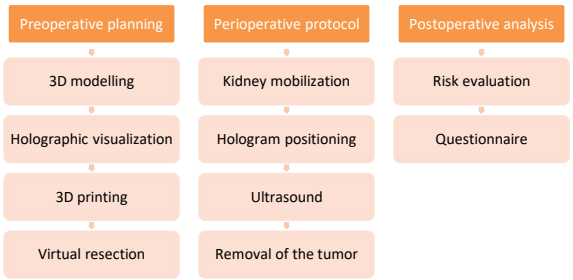

Figure 7-8 Overview of the four different periods for Workpackage 2. The three periods include: preoperative planning, perioperative protocol and postoperative analysis.

As shown in Figure 7-8, the complete protocol is again divided into three periods: preoperative planning, perioperative protocol and the postoperative analysis.

Step 1: Preoperative planning

During the preoperative imaging period, the preoperative MRI of the patient is used to create 3D models with the workflow described by Fitski et al. (2020) and Mimics Innovation Suite (Materialise, Leuven, Belgium). The resulting 3D models are uploaded to the HoloLens to compute the holographic visualization. Additionally we 3D print the 3D model for extra visualization. Furthermore, a virtual resection is performed to get a better sense of the patient-specific anatomy for the upcoming surgery.

Subsequently, we prepare the holographic technique. The surgery is planned in collaboration with the performing surgical team and the research team. Together multiple different anatomical points are digitally defined.

Step 2: Perioperative protocol

Intraoperatively, the standard protocol for a nephron-sparing procedure is followed to free the kidney and tumor from the surrounding tissue. After complete mobilization, stabilization and control of the vasculature the surgeon starts the holographic technique. The different preoperatively digitally planned anatomical points are pinpointed. Then the HoloLens positions the hologram inside the patient. Once the hologram is positioned correctly, the surgeon can look freely at the resulting holograms of the tumor, kidney and artery. Subsequently, the surgeon proceeds the regular NSS procedure. The visualization of the hologram is confirmed or disconfirmed with

intraoperative ultrasound. The tumor infiltration and relationship with the intraparenchymal arteries are confirmed where possible. The surgeon determines the dissection plane and clamps the vessels. Removal of the tumor with a rim of healthy kidney tissue is performed.

Step 3: Postoperative analysis

After the surgery, the surgical team will evaluate the procedure, discuss encountered problems and discuss possible improvements during a process evaluation. Moreover, the surgeon is asked to fill in a questionnaire concerning the workload and user-friendliness. One half of the questionnaire is the NASA-TLX workload questionnaire, commonly used and validated for workload measurements in clinical settings. The other half of the questionnaire is a self-developed questionnaire to understand the user-friendliness and feasibility of the technique. Also, we evaluate how the HoloLens adds to the conventional intraoperative visualization with ultrasound.

Study procedure

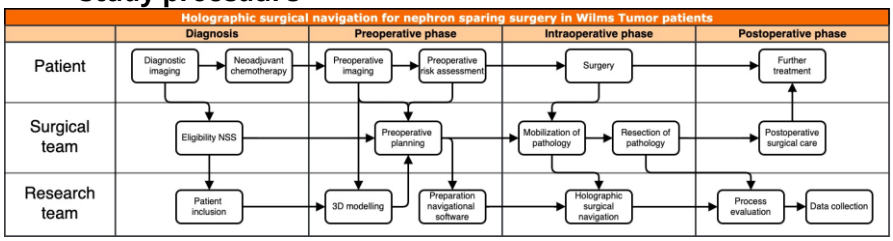

Figure 7-9 Schematic overview of the main procedures of Workpackage 2. The overview is divided into procedures related to the patient, surgical team and research team.

A schematic overview for the main procedures in this study, subdivided into procedures concerning the patient, surgical and research teams, is given in Figure 7-9. After the patient is diagnosed with a renal tumor, the patient receives the standard care as described in the SIOP-RTSG protocol. If the patient is found eligible for NSS by the surgical team, the patient may be included in this study. Subsequently, the preoperative imaging is used to create 3D models, preoperative plan and prepare the holographic navigational software. During the intraoperative phase, the surgeon uses the standard protocol of NSS which requires mobilization and removal of the tumor with a rim of healthy kidney tissue. However, after mobilization of the kidney, the navigation software is used. The holographic navigation software is additional to the conventionally used intraoperative ultrasound as both techniques complement each other.

Postoperatively, the patient continues his or her treatment and the surgeons fill in the provided questionnaires. Additionally, a process evaluation is performed by the surgical team in collaboration with the research team.

Statistics

In this pilot study, we will perform a descriptive analysis with the results of the questionnaires aimed to describe the clinical accuracy, surgical workload and usefulness of the technique. Additionally, we describe the added value of holography in comparison to the normally used intraoperative ultrasound. Results of the pathology report will be included in the analysis.

Ethical considerations

Regulation statement

This workpackage will be conducted according to the principles of the Declaration of Helsinki (3rd edition, 2015) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The described study in this workpackage also is considered a medical device study. All regulatory affairs are like the regulations for workpackage 1. Therefore, the same IMDD and instructions can be used to obtain approval of the METC.

Recruitment and consent

Patients will be recruited by the surgical team. Verbal and written information about the study (patient information letter) will be given to the parents/legal guardian after which they are given a minimum of three days to consider their decision. Written informed consent is asked before inclusion.

Benefits and risks assessment, group relatedness

In this study, we propose to use holograms to guide us during nephron-sparing surgery. Currently, we use intraoperative ultrasound during NSS to get an understanding of the tumor localization, infiltration and the relationship with vasculature. However, ultrasound gives a 2D visualization of the 3D anatomy. The addition of holograms during surgery allows us to visualize this anatomy in 3D which allows for an improved understanding of the patient-specific anatomy. This might be a big benefit for our patients, as it might allow for a higher surgical accuracy which reduces surgical related complications.

In this study, we follow the standard surgical protocol for NSS and use the golden standard for intraoperative anatomic visualization, ultrasound. The addition of holograms is considered safe and does not interfere with the normal procedure. The holograms are only visible through the glasses of the HoloLens worn by the surgeon. They do not harm the patient. Our surgeons will be accustomed to wearing the

HoloLens by the study described in workpackage 1, an earlier phantom feasibility study and phantom practice rounds. Therefore, we do not expect complications for our patients caused by the additional technique.

Compensation for injury

The sponsor/investigator 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.

7.8 DISSEMINATION PLAN

The dissemination plan has two sections, a technical section and a scientific section.

Our self-developed holographic technique will be shared within the pediatric oncologic surgical community. For this, we aim to create an independent app which can be installed on a HoloLens by any user. With a written instruction, other pediatric surgeons will be able to install the application and use it freely.

We aim to share our scientific knowledge through peer-reviewed publications in international pediatric surgical journals. The results of the phantom study will be shared with a detailed graphic instruction how to develop the phantoms. This way other pediatric surgical teams can develop their own phantoms. The results will be shared directly with the oncologic pediatric surgical community. The improvement of our surgical accuracy during nephron-sparing surgery and the possible expansion of the indication for NSS will be presented at the yearly conference of the International Society of Pediatric Oncology. Through this conference, the potential users, oncologic pediatric surgeons, will be informed directly on the findings of this research proposal.

7.9 INTELLECTUAL PROPERTY STRATEGY

In the future, we aim to spread our technique in the pediatric surgical world through an app. We protect our intellectual property (IP) through a lock on our source code. We manage the source code. External parties may obtain licenses to use the app. Through this license management strategy, we keep control of how the technology works and protect the knowledge obtained in this project. Thus, we share the

technique with colleagues without sharing vital components and knowledge. Licenses will be managed in collaboration with the transfer office of our center.

7.10 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

Administrative aspects, insurance and monitoring

The Princess Máxima Center is responsible for the handling, administration and storage of the data. The Trial and Data Center (TDC) safeguards this process within our center. They provide a central data manager who will structure the database and electronic Case Report Forms (eCRFs). The PhD-student will assist the data manager and fill in the eCRFs.

The Princess Máxima Center has a patient insurance for every patient participating in the studies of workpackage 1 and 2.

Trial management is supplied by the TDC to ensure the quality of the performance of the study. Monitoring is required for the clinical study in the third workpackage, which is subjected to the WMO. The Julius Center of the UMCU provides monitoring for studies performed in the Princess Máxima Center under the TDC.

Handling and storage of data and documents

The TDC supplies CastorEDC databases for this proposal. CastorEDC is an ICH-GCP compliant clinical data management platform. Within CastorEDC, electronic Case Report Forms (eCRFs) are made to store the clinical and questionnaire data. Results from the filled in paper questionnaires are put into the CastorEDC by the data manager or PhD-student and subsequently stored in a locked record cabin by the data manager. Only the research team and the data manager will have access to the source data. All data within CastorEDC is pseudonymized, with a key-file stored remotely by the data manager. Clinical and imaging pseudonymized data will be supplied by the Data Access Biobank Committee of the Princes Máxima Center. Imaging data will be stored in SURFdrive. SURFdrive is an encrypted cloud service capable of safely storing all MRI files of our patients. The used folder in SURFdrive is only shared with the research team, surgeons, technical physician and data manager. All data in the CastorEDC, paper questionnaires and SURFdrive, will be stored for 15 years.

7.11 BUDGET DESCRIPTION

Year	PhD Student	Sr Scientific Personnel	MBO*	HBO*	Academic*	PhD Student	Sr Scientific Personnel	MBO	HBO	Academic	Total	Addit. Personal Budget
1	1.00	0.00	0.00	0.00	0.00	52,509.00	0.00	0.00	0.00	0.00	52,509.00	750.00
2	1.00	0.00	0.00	0.00	0.00	63,257.00	0.00	0.00	0.00	0.00	63,257.00	750.00
Total	2.00	0.00	0.00	0.00	0.00	115,766.00	0.00	0.00	0.00	0.00	115,766.00	1,500.00

* Non-Scientific Personnel

Year 1	
Description	Amount
HoloLens 2	4,600.00
Ultimaker S5 3D printer	5,000.00
Materialise Mimics Innovation Suite segmentation software	6,000.00
Phantom building materials	4,000.00
3D printed stainless steel surgical tools	3,600.00
METC review	3,000.00
METC non-WMO assessment	500.00
Trial and datamanagement services	16,710.40
Surgical tools	3,000.00
Advanced computer	3,000.00
	49,410.40

Year 2	
Description	Amount
Materialise Mimics Innovation Suite segmentation software	6,000.00
3D printing materials	500.00
	6,500.00

Year	Year 1	Year 2	Total
Personnel	52,509.00	63,257.00	**115,766.00**
Addit. Personal Budget	750.00	750.00	**1,500.00**
Materials	49,410.40	6,500.00	**55,910.40**
Services	0.00	0.00	**0.00**
Open Access	6,000.00		**6,000.00**
Internat. internship	0.00		**0.00**
Total	**108,669.40**	**70,507.00**	**179,176.40**

The budget for this proposal has been drawn up in collaboration with a project controller.

7.11.1 Personnel costs

The estimated total duration of this proposal is expected to be 24 months. The PhD-student will work for the complete duration of this proposal (1.0 FTE). The PhD-student is responsible for organizing workpackages 1 and 2 and implementation of the HoloLens technique. Additionally, the PhD-student will assist the data manager, analyze the obtained data and write the manuscripts. This is considered a complete project. Other projects of the PhD-student will be funded through our own contributions.

Additionally, we require the services of the internal service provider Trial and Data Center (TDC). Trial support startup costs include trial support (€720 for 12 hours) and database support (€5000 for CastorEDC supervision and randomization module ALEA). Management of the study includes supervision by a trial manager (€5400 for 90 hours), research nurses (€300 for 5 hours) and monitoring by Julius Central (±€3500, we are awaiting the formal quotation). Including taxes, the total costs of the TDC combine to €16.710,40.

Materials

Devices and licenses:

We request a HoloLens 2 which will be used in this study at a cost of €4600.

Materialise Mimics Innovation Suite is used to segmentate the MRI data and create the 3D models used by the HoloLens. We request a year license for this software for the duration of this proposal, 24 months, costing 2x €6000.

We will need to 3D print surgical tools in stainless steel which can be recognized by the HoloLens. These stainless-steel tools are estimated to cost €3600.

Additional costs

Open Access publication:

We expect to publish our results in open access journals and request €7000 for the publication of two manuscripts.

Medical Ethics Review Committee:

The fee of the METC of the UMCU for the review of the research protocol of workpackages 1 and 2 is €6000.

Accountant:

The services provided by the accountant are estimated to cost €2500.

7.12 DEVELOPMENT PLAN

After completion of this project, we aim to consistently implement this holographic technique during nephron-sparing surgery. We have designed the workpackages with this in mind. In workpackage 1 we ensure that the technique performs consistently during real clinical use without risks for our patients. Together with the pilot implementation study in workpackage 2, we expect implementation will be achievable.

Currently we only perform NSS on unilateral WT patients in a very small subset of patients. Yet if NSS is performed successfully, it may reduce long-term complications such as end-stage renal failure. If we can broaden the eligibility for NSS because we have improved our technique, we can increase the number of patients eligible for NSS. Thus, we can prevent more long-term complications in our patients.

Based on this work, we will also aim to implement the technique in other pediatric oncologic surgical procedures. We expect this technique may be of added value for neuroblastoma, sarcoma, and hepatoblastoma surgery. In these procedures, an accurate visualization of the anatomy is crucial to prevent complications. At first, further implementation in different surgical procedures will be studied in a research pilot environment. This can easily be realized without our small surgical team.

7.13 OPPORTUNITIES AND RISKS

Broadening the assessment criteria for the use of NSS in unilateral Wilms' tumor patients is considered controversial. We will only be able to do this if we are sure that our technique helps improve the tumor resection. When the use of holograms has proven to be of help, we will disseminate the software to our collaborative partners abroad so they will be able to use this technique within the current accepted indications. Once the experience with hologram-based surgery is increasing then we will be able to expand the indications for NSS.

We also aim to use the technique for other pediatric surgical procedures. With this in mind, we have developed the technique to be independent of the anatomy of the patient. The development of the 3D kidney models can also be performed for other anatomic structures. Positional landmarks are based on anatomical landmarks which are not specific to kidney tumors. This ensures that the algorithm works without being limited to nephron-sparing surgery. The algorithm can be applied to any type of open surgical procedure if necessary. We do not foresee risks with this future opportunity.

In the future, we hope to develop the holographic technique as a reliable clinical tool with multiple indications for its use. However, clinical implementation requires the software to be CE-certified. This CE-certification process is extensive. It requires additional scientific studies and an Investigational Medical Device Dossier (IMDD). The current proposed studies contribute to obtaining a CE-certification but more studies will be necessary. Therefore, CE-certification is a future possibility which does not require anticipating action right now. For the future work on the IMDD, we have consulted a business developer and the department of Information, Data and Technology Healthcare department in our center.

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Chapter 8 Nephron-sparing surgery for pediatric renal tumors after centralization of pediatric oncology care in the Netherlands: improved outcomes with 3D modeling

This chapter is based on

Fitski, M., Bökkerink, G. M., van Peer, S. E., Hulsker, C. C., Terwisscha van Scheltinga, C. E., van de Ven, C. P., Wijnen, M. H., Klijn, A. J., van den Heuvel-Eibrink, M. M. & van der Steeg, A. F. *(Under Review).* Nephron-sparing surgery for pediatric renal tumors after centralization of pediatric oncology care in the Netherlands: improved outcomes with 3D modeling.

8.1 ABSTRACT

Background and aim

Nephron-sparing surgery (NSS) for nonsyndromic unilateral Wilms tumor (nsuWT) is not commonly performed and only after following strict guidelines. However, long-term follow-up studies raise the concern of increased risk of renal dysfunction after total nephrectomy. To increasingly perform NSS for nsuWT patients, we must first understand the influence of experience and innovations for this type of surgery. In this retrospective single center cohort study, we summarize and report the surgical outcome of NSS since centralization of pediatric oncology care in the Netherlands, and implementation of new technological advancements.

Methods

We retrospectively assessed all NSS procedures from January 1st 2015 until January 1st 2024 for patients who underwent surgery for a renal tumor at the Princess Máxima Center for Pediatric Oncology. Data were gathered on patient characteristics, diagnostic information, radiological characteristics, surgical technique and use of innovations, postoperative outcome, administered treatment and surgical follow-up.

Results

36 patients (58.3% female, 41.7% male) were included with a combined total of 43 NSS procedures. Mean (SD) age at diagnosis was 33.3 (23.1) months. 27 procedures were preoperatively planned with a 3Dmodel and of these 27, only 1 (3.7%) unexpected positive margin occurred. 16 procedures were performed prior to introduction of 3D models, of which 3 (18.8%) resulted in an unexpected positive margin.

Conclusions

In this retrospective single center cohort study, we show an excellent surgical outcome after NSS for children with renal tumors after the implementation of 3D models. This study can act as a baseline cohort to harmonize preoperative assessment, intraoperative technique and implement of innovative surgical technology for further expansion of NSS for nsuWT patients.

8.2 INTRODUCTION

Renal tumors in children represent 6% of all childhood cancer types and occur in roughly 35 patients annually in the Netherlands. Here, patients are treated according to the SIOP-RTSG-2016-UMBRELLA treatment protocol (further referred to as UMBRELLA) designed by the International Society for Pediatric Oncology Renal Tumor Study Group (SIOP-RTSG) [1]. Surgical resection of the tumor is a key component of this treatment protocol. Surgical resection can be carried out by either completely resecting the kidney containing the tumor (total nephrectomy, TN) or by resecting the tumor while preserving non-affected functional kidney tissue (nephron-sparing surgery, NSS). For most patients with unilateral disease without a genetic predisposition syndrome or anatomical aberrations (nonsyndromic unilateral Wilms tumor; nsuWT), neoadjuvant chemotherapy followed by TN is the standard of care with excellent overall survival in recent decades [2]. NSS is preferred in patients with bilateral disease and/or a genetic predisposition syndrome. However, the SIOP-RSTG 2001 treatment protocol allows NSS for nsuWT under strict conditions which led to a rise of NSS being performed since its implementation [3]. More than TN, NSS carries an inherent oncological risk of incomplete resection (also described as a positive surgical margin or R1 resection) with an increased risk of local recurrence. Incomplete resections still occur in ±15-35% of cases internationally, necessitating more intensive chemotherapy and the addition of radiotherapy, to reach satisfactory overall survival [4–6]. Thus, these strict guidelines ensure oncological safety and surgical prudence when considering NSS.

Recent long-term follow up studies have raised concern about the consequences of TN for unilateral WT patients (nsuWT) [7–12]. Patients treated with TN for nsuWT by the Children Oncology Group (COG) treatment protocol have a 2.4% cumulative incidence of renal dysfunction after 35 years follow-up [8, 13]. This incidence may even increase later in life [10, 14]. For this reason, there is discussion on expanding the indication for carrying out NSS [15–20]. Moreover, the experience with NSS has grown in recent years and the surgical field has seen an increase in technical innovations such as the use of intraoperative Ultrasound (ioUS), 3D modeling, and fluorescence-guided surgery [21, 22]. These advances aim to improve surgical outcome my minimizing the risk of positive surgical margins. However, to safely expand the applicability of NSS for nsuWT patients, we must first study how these recent technical advancements have influenced surgical outcome.

In November 2014, pediatric oncology care was centralized into one national center. Since then, one surgical team has been performing all surgical procedures for pediatric oncology patients in the Netherlands. Experience with rare surgical procedures such as NSS has greatly improved. Furthermore, we implemented the use of ioUS and 3D modeling for NSS in 2018 and 2019, respectively. An example of 3D imaging is shown in Figure 8-1. 3D models are based on a semi-automated delineation of important anatomical structures in the 2D MRI. This improves the perception of tumor location, depth and relationship with important structures [23]. With ioUS, surgeons use 2D ultrasound directly on the kidney parenchyma to locate the tumor and determine the resection border. Thus, our surgical cohort since centralization of pediatric oncology care allows us to study the result of both increased surgical experience and technical advancements for NSS for WT patients. The multidisciplinary setup of our pediatric renal tumor care after centralization has previously been described [24, 25].

In this retrospective single center cohort study, we aim to summarize the experience of our surgical team and report the surgical outcome of NSS since centralization and implementation of technological advancements. This can be used as a baseline outcome measurement and to develop new surgical studies that may enable further expansion of NSS in the future.

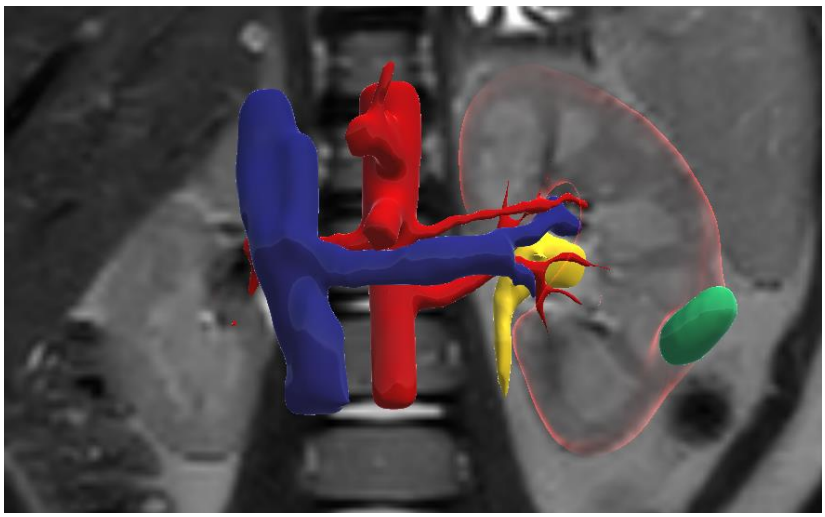

Figure 8-1 3D model of a patient with a left sided kidney tumor who was treated in the Princess Maxima Center with nephron-sparing surgery. The kidney is transparent, on order to show the relationship between the intraparenchymal vessels and the tumor.

8.3 METHODS

We retrospectively assessed all nephron-sparing procedures from January 1st 2015 until January 1st 2024 in the Princess Máxima Center for Pediatric Oncology. Patients were included if informed consent for retrospective scientific research had been given. Information was gathered of patient characteristics including underlying genetic predisposition syndromes, diagnostic information including biopsies, radiological characteristics, surgical technique, postoperative outcome, administered treatment and follow-up including metachronous disease and further management including radiotherapy (EudraCT numbers 2007-004591-39, 2016-004180-39, MEC 202.t34/2001/122, MEC-2018-026).

NSS procedures were characterized per patient and per kidney. We did not include patients whose nephron-sparing procedure was intraoperatively converted to TN. Information on initial staging and neoadjuvant chemotherapy was collected for each patient. Any change in neoadjuvant chemotherapy regimen was recorded. Moreover, tumorboard notes were analyzed to determine the operative plan.

Per kidney, tumor volume at diagnosis and before surgery were determined, either as mentioned in the radiology report or using measurements of the radiologist and the formula: (length * width * height) * 0,523. Intraoperatively, we recorded which surgical techniques were used such as vascular clamping, cooling with an ice bath and intraoperative ultrasound. Moreover, we looked at handling of the urine collection system (UCS) and any drains left in situ. Postoperatively, we assessed complications, local staging, histological subtypes, margin status and lymph node status. Specimens with nephroblastomatosis (NB) or nephrogenic rests in the resection margin were considered radical. All surgeries were performed by the same surgical team, including two pediatric surgeons (KvdV and AvdS) and one pediatric urologist (AK).

To determine the influence of new technologic advancements (ioUS and 3D modeling) on NSS, we compared the surgical procedures with and without the use of 3D modeling for preoperative planning. 3D modeling for NSS has been implemented as standard of care in our center in March 2019, with one pilot case in July 2018.

8.4 RESULTS

Patient characteristics are summarized in Table 8-1. 36 patients (58.3% female, 41.7% male) were included. Mean (SD) age at diagnosis was 33.3 (23.1) months. Mean (SD) follow-up was 46.5 (29.8) months. One patient (stage V) died after 18 months follow-up (deceased at the age of 73 months).

A large proportion of patients (63.9%) were initially diagnosed as stage V. 29 patients were screened for a predisposition syndrome, of whom 19 (65%) were found to have one. Beckwith-Wiedemann syndrome was diagnosed most frequently (10/19, 53%). Seven patients had metachronous disease.

A combined total of 43 NSS procedures was performed (mean (SD) NSS procedure per patient = 1.22 (0.42)) including 13 unilateral cases (14 procedures) and 23 bilateral cases (29 procedures). For two NSS procedures, we could not recover the operative notes, and thus data on intraoperative details are incomplete. Forty-three NSS procedures were included. Twenty-three (53.5%) were left-sided, 18 (41.8%) were right-sided and two (4.6%) were performed on a horseshoe kidney. Tumors had a median (IQR) volume at moment of diagnosis of 11 (5-66) ml and a median (IQR) volume of 2.5 (0.75-19.5) ml before surgery. Most (27, 62.7%) procedures were preoperatively planned with a 3D model (62.8%). Surgical characteristics of NSS procedures with or without a preoperative 3D model are shown in Table 8-2. Median (IQR) blood loss was 75 (32.5- 135) ml per procedure. In roughly halve of the procedures (22, 51,2%), the vessels were clamped for a mean (SD) ischemia time of 19.43 (14.74) minutes. Seven procedures (16.2%) had a surgical positive margin and in three procedures (7%) there were lymph nodes positive for tumor infiltration. Ten patients received postoperative flank radiotherapy (RT); three patients because of a positive surgical margin, 4 patients due to positive lymph nodes, 2 patients had both positive surgical margin and lymph nodes, and 1 patient had high risk sinus invasion. No patient had a local recurrence during follow-up.

Table 8-1 Patient characteristics of all patients undergoing nephron-sparing surgery between January 1st 2015 and January 1st 2024, stratified by initial staging: unilateral and bilateral.

Patient Characteristics		**Unilateral**	**Bilateral**	**P-value**
n		13	23	
Patient sex	Female	8	13	1.000
	Male	5	10	
Number of NSS of procedures (mean (SD))		1.08 (0.28)	1.26 (0.45)	0.191
Age at Diagnosis (months, median [IQR])		27.0 [19.0, 44.0]	24.0 [13.5, 52.5]	0.768
Follow up after surgery (months, median [IQR])		54.0 [25.0, 65.0]	50.0 [21.50, 59.5]	0.899
Diagnosis (%)	CMN	1 (7.7)	0 (0.0)	0.046
	CN	3 (23.1)	0 (0.0)	
	NB	1 (7.7)	2 (8.7)	
	Wilms	8 (61.5)	21 (91.3)	
Direct surgery (%)		4 (30.8)	0 (0.0)	0.032
Metachronous disease (%)	No	12 (92.3)	17 (73.9)	0.368
	Yes	1 (7.7)	6 (26.1)	

Table 8-2 Surgical characteristics of all nephron-sparing surgery procedures between January 1st 2015 and January 1st 2024, stratified in two groups, without or with preoperative planning with a 3D model.

Surgery Characteristics	Planned with 3D model:	No	Yes	P-value
n		16	27	
Affected kidney	Horseshoe kidney	1	1	0.545
	Left	10	13	
	Right	5	13	
number of tumors (median [Min, max])		1.0 [1.0, 4.0]	1.0 [1.0, 5.0]	0.504
Preoperative planning				
Tumor volume diagnosis (cc, median [min, max])		15.5 [1.0, 1360.0]	13.0 [0.0, 1379.0]	0.403
Tumor volume before surgery (CC, median [min, max])		5.0 [0.0, 279.0]	1.5 [0.0, 360.0]	0.125
Suspect for NB	No	12	16	0.474
	Yes	4	11	
Intraoperative technique				
Blood loss (CC, median [IQR])		155.0 [0.0, 350.0]	50.0 [20.0, 250.0]	0.099
Vascular clamping	No	7	12	0.929
	Yes	8	14	
Duration of clamping (minutes, median [IQR])		15.0 [10.0, 20.0]	15.0 [5.0, 61.0]	0.783
Parenchyma cooling with ice bath	No	0	20	0.124
	Yes	0	6	
Intraoperative US	No	7	4	0.088
	Yes	8	22	
Surgical outcome				
Margin status (%)	Negative	13 (81.2)	23 (85.2)	1.00
	Positive	3 (18.8)	4 (14.8)	
Expected positive margin	No	3	1	0.114
	Yes	0	3	

Positive surgical margins

Seven (16.2) NSS procedures resulted in incomplete resections of the renal tumor. There was a significant difference in median preoperative tumor volume between the negative (1.00 ml) and positive surgical margin (66.00 ml) groups (p = 0.035). There was a longer ischemic time between both groups (negative surgical margin mean = 17.33 minutes, positive surgical margin mean = 27 minutes). Results of surgical outcome per calendar year are shown in Figure 8-2.

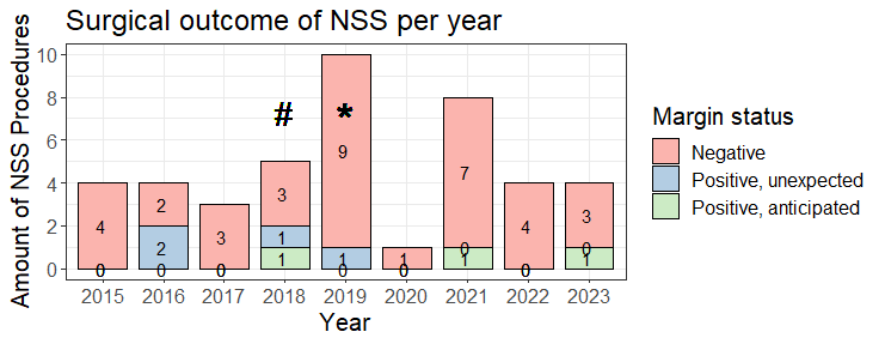

Figure 8-2 Surgical outcome of nephron-sparing surgery (NSS) procedures for children with renal diseases in our center. **#** = introduction of ioUS, september 2018; ***** = introduction of 3D modeling, march 2019.

In four patients, the positive surgical margin was unexpected. Two patients were treated with vincristine – actinomycin D (VA) and flank radiotherapy, one patient with VA only. They are in complete remission. One patient deceased 18 months postoperatively due to complications from dialysis.

In the other three patients, the positive surgical margin was anticipated and preoperatively planned in a multidisciplinary board. In order to preserve a viable amount of functional renal parenchyma and to prevent dialysis, these patients underwent an enucleation procedure. There were no local recurrences in these patients, and they are all in complete remission

NSS for unilateral disease

Fourteen (32.5%) NSS procedures were performed on 13 patients with unilateral disease, or disease in a horseshoe kidney. One patient had two separate NSS procedures for two different tumors in the same kidney. Five of these 13 patients were diagnosed with a predisposition syndrome, four patients had not been not screened. Two patients had a single kidney (one because of prior total nephrectomy and one because of a congenital single kidney), for which enucleation

was performed resulting in an anticipated R1 resection. There was one unexpected positive surgical margin in this patient group. This patient was not preoperatively planned with a 3D model and had a large upper pole tumor volume (140ml) at the time of surgery. In one patient, the urine collection system was opened unexpectedly. All NSS procedures for nsuWT patients planned with 3D modeling had a complete resection (N = 5) without positive surgical margin.

8.5 DISCUSSION

In this retrospective single center cohort study, we have a good outcome after NSS for kidney tumor patients, after a mean 46.5 (SD 29.8) months follow-up post-surgery. In our cohort of 43 NSS procedures, seven NSS procedures (16.2%) resulted in a positive surgical margin of which three were expected. R1 procedures received additional postoperative chemotherapy and flank radiotherapy. No re-resections were performed nor were there any local recurrences, possibly indicating low risk as shown in other studies [4, 26–28]. One patient died of complications during dialysis.

There was a trend in difference in surgical outcome between the group with and without preoperative planning with 3D modeling yet not significant. However, all 3 procedures with were preoperatively planned with a 3D model to assess the feasibility of enucleation, avert a total nephrectomy and dialysis. We started with the use of 3D modeling in March 2019, after one pilot case in July 2018 [22]. In this group of 27 procedures planned with 3D modeling, there was only one unexpected positive surgical margin (3.7%). This is an excellent outcome and shows improvements compared to the group without 3D planning (18.8%, p = 0.114). Also, the blood loss per procedure appears lower in the patient group planned with a 3D model (median 155 vs 50 ml, p = 0.099) Especially in patients with larger tumors who require NSS, extensive preoperative planning with 3D modeling helped to assess the feasibility of a complete resection. If an irradical resection is anticipated based on this preoperative planning with 3D models, the patient and treatment team can be informed beforehand. Moreover, the improved vascular understanding with 3D modeling helped to plan the use of an ice bath for prolonged ischemic time in two cases. In smaller tumors, it can be useful to predict opening of the UCS and feasibility of using pressure for local ischemia instead of vessel clamping, minimizing ischemic time.

With the combination of ioUS and 3D technology, surgical outcome appears to have improved compared to the cohort operated without. The usability of these techniques may further improve through developments in the field of 3D modeling and ioUS. For example, 3D

modeling can be used to create patient-specific phantoms for simulation surgery to gain more experience [29, 30] but also holographic preoperative planning and intraoperative guidance [31, 32] are possibilities. Electromagnetic navigation through tracked ioUS registration may also help guide the surgeon during NSS [33, 34]. Initial results of fluorescent-guided surgery for NSS are interesting especially for direct intraoperative margin assessment, showing an inverse tumor-to-kidney infrared signal [35]. Thus far we have not implemented fluorescent-guided surgery for NSS in our center.

After implementation of the technical advancements, there has been one unexpected positive surgical margin. Based on the preoperative imaging, the 3D model and ioUS, the capsuled lesion was located and removed with adequate margin. Unfortunately, active tumor cells were recognized in the rim of kidney tissue with nephroblastomatosis resulting in an R1 resection. It was impossible to distinguish WT from nephroblastomatosis both pre- and intraoperatively, yet this is crucial for complete resections. Hopefully, new preoperative imaging techniques such as MRI DWI / ADC component analysis will help to further distinguish this difference in the future [36, 37].

Looking specifically at the group of nsuWT patients planned with 3D modeling (N = 5), there were no incomplete resections. These patients were treated safely with NSS and thus have the benefit of improved renal function and possible decreased risk of renal diseases later in life. As no oncological risk should be taken for these patients, extensive preoperative planning is imperative. The surgical planning with a 3D model helped to assess the feasibility of NSS and ensured we were confident of a complete resection, minimizing oncological risk.

Apart from the technical advancements, one of the expected main contributors to this decrease in unexpected positive surgical margins is the centralization of care. Before centralization of pediatric oncology care in November 2014, five NSS procedures were performed in the Netherlands each year, divided among six pediatric surgical centers in the country. After centralization, our surgical team consisting of two dedicated NSS surgeons with one pediatric urologist have performed all NSS procedures in the Netherlands. It is expected that this has improved our surgical handling of the kidney, reduced ischemia time, and improved surgical confidence . For example, centralization has also allowed us to become acquainted with ioUS for NSS. This technique has been used in at least 30 out of 43 procedures and consistently after implementation as standard of care (69.7%). Aldrink et al. also reported routine use over time, now using ioUS in every NSS procedure, and highlight its importance for surgical mapping [26]. However, they also

mention that experience with ioUS is crucial to reduce positive surgical margins. In our cohort, this technique combined with 3D modeling and improved surgical experience has reduced our unexpected positive surgical margins. Since its use, our surgeons do not operate without both techniques. Therefore, we advocate to perform NSS in experienced reference centers to ensure the best surgical outcome.

This study has several limitations. Firstly, this is a retrospective single center cohort study in which we compare two groups within in the same cohort. These groups were not prospectively randomly assigned. Secondly, pediatric oncology care centralized into one national center. Therefore, results from our center may not be directly translatable to other centers for which care is not centralized. Lastly, we decided not to include patients whose nephron-sparing procedure was intraoperatively converted to TN which may have introduced a selection bias.

The overview in this study can help to expand the use of NSS for nsuWT patients in the future. The results show that with adequate experience and appropriate use of technological innovations, excellent surgical outcomes can be obtained for Wilms Tumor patients. This holds true for both bilateral and unilateral disease. Thus, further surgical expansion of the current oncological guidelines may be performed safely if preoperative assessments and intraoperative techniques are harmonized between surgeons [15, 19, 28]. This ensures surgical teams perform consistently and oncological risks are decreased. Moreover, patients should be treated in specialized reference centers to make use of concentrated surgical experience [20].

8.6 CONCLUSION

In this retrospective single center cohort study, we show an excellent surgical outcome after nephron-sparing surgery for children with renal tumors after implementation of technological advancements such as 3D models and ioUS. This study can act as a baseline cohort to harmonize preoperative assessment and intraoperative technique for further expansion of the NSS for nsuWT patients.

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Chapter 9 General discussion and future perspective

In this thesis, improvement of the applicability of nephron-sparing surgery for patients with Wilms tumor has been studied through two approaches: improving international collaboration among surgeons and the implementation of 3D technology. This chapter reflects on this work and discusses the impact of 3D technology and possible clinical implications. Moreover, we will describe future directions for this line of care and research.

9.1 PEDIATRIC ONCOLOGIC SURGERY AND 3D TECHNOLOGY

3D imaging techniques are relatively new in surgery, but application has been growing rapidly. In adult surgery, implementation started with primarily with 3D imaging of bones in head and neck surgery, neurosurgery, and orthopedic surgery. This application has been driven by the ease of bone segmentation on CT, the accuracy of the preoperative and intraoperative correlation of these rigid structures and the formation of 3D labs in hospitals. Studies with clinical implementation of 3D imaging have shown improvements of surgical safety, precision, and surgical confidence and are expected to improve clinical outcomes (1–3). In adult soft tissue surgery, 3D imaging is now more and more used in the fields of oncologic liver and pelvic surgery, urology, and cardiothoracic surgery. However, 3D imaging for soft tissue surgery has not been adopted on a large scale yet. 3D imaging of these soft tissue components still requires manual or semi-automated segmentation which increases labor costs, introduces inaccuracies due to observer dependency and requires more specific costly software. In the field of pediatric oncologic surgery, all these limitations are significantly worse (4). This is related to the inherent rarity of the diseases, technical innovations and clinical research in this field develop relatively slow. Research is scarce in this very narrow surgical subspecialty and only a few surgical departments around the world are working on implementation of this technology. Moreover, as our patients vary in age and thus physical development, all technical solutions require very patient-specific tailored approaches. These individualized approaches are difficult to harmonize which is essential to overcome limitations as shown in 2.8 and for large scale adaptation (5,6).

In adult urologic surgery, 3D imaging has been primarily used for surgical planning of oncologic renal surgery (7–9). In most cases, the goal is to get a clear understanding of the tumor location and relationship with the vessels to assist in complete tumor resection and to avoid excessive removal of functional renal parenchyma. 3D imaging

intuitively visualizes a reconstruction of the patient-specific anatomy, which is a difficult cognitive task based on 2D imaging alone.

In a study performed by Wake et al., surgeons performed poorly when mentally reconstructing cross-sectional imaging data into a 3D digital environment (10). After assessing cross-sectional imaging data (CT or MRI), experienced surgeons were asked to position a matching 3D tumor in the 3D kidney in an experiment appropriately called "Pin the tumor on the kidney". Assessment of the overlap of the position of the 3D tumor with the actual segmentation through the dice similarity coefficient (DSC, ranging from 0 to 1), there was no overlap in 26.67% of cases and the overall DSC was 0.277 ± 0.248. This is remarkably low. This score increased significantly when surgeons reviewed the cases with a 3D printed model (DSC of 0.796 ± 0.090). Similar results were found in neurosurgery, also showing improved spatial understanding by experienced surgeons when using 3D modelling for preoperative planning (11).

Improvement of the patient-specific understanding can improve surgical confidence. In this way, 3D models help in determining the appropriate surgical approach and can predict volumetric outcomes (Chapter 5), especially for partial nephrectomy (12–16). However, clear positive clinical results remain scarce. Possibly due to the relatively difficult adaptation, only a few randomized controlled trials (RCT) have been performed on the use of 3D imaging for adult partial nephrectomies. Shirk et al. reported on a multicenter RCT in which 92 patients were included (17). Patients in the intervention group (44) underwent robot-assisted partial nephrectomy, planned with 3D models visualized in virtual reality (VR). Patients planned with VR had a significantly lower operative time, less blood loss, shorter duration of clamping of the vessels and lower length of hospital stay. Zhang et al. published a RCT on the use of 3D imaging for planning of laparoscopic partial nephrectomy including 30 patients in total. They also report a decreased surgery time and reduced estimated blood loss in patients who were surgically planned with 3D imaging. Even though results were significant, the patient numbers in both groups were very small due to limitations of the technique (18). Bianchi et al. performed a prospective nonrandomized trial in which they included 195 patients with cT1-T2 renal masses (1). They showed an improved surgical outcome in the group of patients who had been surgically planned with a CT and a 3D model in comparison to only a CT. Interestingly, they significantly reduced the number of intraoperative conversions from partial nephrectomy to total nephrectomy with 3D modelling. Unfortunately, they did not randomize between the groups and only used stratification. Moreover, they also report on large differences in quality of the 3D

models due to inherent variance in image quality and segmentation processes. Larger RCTs require more standardized imaging, segmentation and visualization approaches for further implementation of 3D imaging in adult oncologic surgery and to further study the true clinical impact of this technology (19).

As pediatric renal tumor surgery has a vastly different approach from adult renal tumor surgery, results from adult studies may not be directly translated to pediatric surgery. Firstly, tumor biology and oncologic (neo)adjuvant treatment protocols differ significantly between children and adults. Secondly, surgical experience with this type of surgery is much smaller in pediatric surgery due to relatively small number of patients, especially for nephron-sparing surgery. Thirdly, we usually perform renal surgery in an open transperitoneal abdominal approach, whereas surgery in adults is typically performed laparoscopically or robotically. Looking specifically at partial nephrectomy, pediatric surgeons take very few risks in patients with unilateral tumors, but at the same time are willing to perform very large resections in patients with bilateral tumors to ensure a minimum amount of functional renal parenchyma and prevent kidney transplantation. These nuances in pediatric surgical decision making must be considered during development and evaluation of new (3D) techniques. For this reason, we developed an MRI based 3D imaging workflow in 2.8 instead of CT commonly used in adults. Besides, we developed a registration technique with holographic 3D augmented reality (AR) suitable for open renal surgery instead of on-screen 2D AR which can be implemented in the screen of the laparoscope or Da Vinci display (Chapter 7).

Unfortunately, there still is a lack of objective clinical evidence for 3D technology implementation in pediatric renal tumor surgery. This can partially be explained by the lack of patients in our center as we treat only 35 renal tumor patients each year, of which only 5 to 9 per year are surgically treated through partial nephrectomy. Even if we accept a small cohort in a study like Zhang et al, it will take roughly 4-6 years to obtain 30 patients in the Netherlands. By that time, the experience of our surgeons and technology will have advanced and improved, making it difficult to compare patients within the cohort. Additionally, 3D models primarily improve patient specific anatomical understanding of the surgeon. This leads to improved confidence and surgical accuracy, which are indirect results of this technique as shown in Chapter 8.

Looking at the technology, there are two primary techniques which could be developed further: patient-specific simulation surgery and intraoperative holographic guidance. With patient-specific hydrogel phantoms, the surgeons were able to visualize the surgical plane

described with virtual resections and perform the surgical approach (Chapter 6) (20). Moreover, these personalized phantoms were a valuable communication tool for the surgical team. The hydrogel phantom accurately mimics kidney tissue handling, US imaging and surgery. Yet there were technological limitations for this approach which need to be addressed, such as long development times, difficult multi-material 3D printing, no fixation of the tumor and instability of the vasculature. These limitations are common in hydrogel simulations and a big drawback (21–23) and hinder further development of simulation surgical approaches. To overcome these limitations, others have proposed the combination of rigid vasculature printing with silicone casting, or simply not including the vessels at all (24,25). Neither of these are actual solutions as they have their own limitations. Further development should focus on a multistep hydrogel casting method as proposed by Saba et al., a group well known for their urologic simulation methods (26). In this method, internal renal anatomy is also casted in hydrogel instead of 3D printing. This combined approach can have a big impact on pediatric nephron-sparing surgery allowing for muscle memory, improve patient-specific understanding and as a communication tool as shown in our initial implementation of the technique. Yet focus should lay on the use of these models for research and training. For example, we could use phantoms to practice laparoscopic nephron-sparing surgery in children (22,24). Currently there is no indication for laparoscopic NSS in children while this is the most common approach in adults. This is primarily caused by the lack of patients combined with a lack of experience with laparoscopic approaches for renal tumors in children. Thus, it is practically impossible to overcome the learning curve, increasing patient risk for an already delicate approach. By training on patient-specific phantoms, including the simulation of the pediatric abdominal cavity, we can overcome the learning curve before performing NSS in children. Therewith we may be able to introduce the positive effects of laparoscopic NSS, without taking more oncological risk compared to the open approach (27).

Based on this thesis, we believe that our future efforts should focus on intraoperative holographic guidance for open NSS. In the coming year we finish the first study described in the research proposal in Chapter 7. Hopefully, this will result in more knowledge on holographic guidance for renal tumor surgery, operating with a HoloLens and provide suggestions on how to take this further. We have set harsh rules to continue the development of holographic navigation for renal tumor surgery. These goals are related with accuracy (<5 mm mean error), user-experience (low workload), time (< 10 min per registration) and consistency (After testing, > 5 consecutive successful

procedures). We have done so to ensure that the technique is feasible and appropriate to use for NSS. If we can reach these goals, we should start with a clinical pilot study for the use of AR during NSS.

9.2 SURGICAL IMPROVEMENT FOR PATIENTS WITH WT

Given the high cure rate of WT patients (±90%), efforts are now also focusing on reducing long-term complications for these patients. Especially for nonsyndromic unilateral WT patients (nsuWT), the oncological outcome is excellent with an OS of roughly 95% (28). However, the long-term consequences of treatment show treatment related late effects such as an increased risk of chronic kidney disease and cardiovascular problems (29). The applicability of NSS for these nsuWT patients can be of particular interest to possibly improve long-term renal function and reduce complications (30). To define which of these patients might be eligible for this type of surgery, we have first sought international surgical consensus in Chapter 2. Through a Delphi method, we aimed to answer the question "When to perform NSS for patients with Wilms Tumor" and propose consensus-based statements on this topic. The expert panel defined over 45 statements on five different topics. These statements also sparked a larger debate as the statements were based on the expert opinion of surgeons, not directly based on data. Thus, more data is required to validate these statements.

The biggest concerns about these statements are related to the oncological risk of NSS for unilateral nonsyndromic renal tumors (31). As a total nephrectomy is standard of care for most cases, the advantages of NSS should significantly outweigh the oncological risks. However, these advantages of NSS remain unclear and even the long-term disadvantages of TN remain unclear. It is known that patients with a solitary remnant kidney after treatment of a pediatric renal tumor have a lower estimated Globular Filtration Rate (eGRF) and a higher perfusion rate, leading to a higher blood pressure. It is thought that these decreased functional capacities increase the risk to develop renal injury over time, later in life (32–34). In a larger cohort study of Dutch Childhood Cancer Survivors, patients requiring a total nephrectomy were at risk for a reduced eGFR (33). However, other treatment related factors such as abdominal radiotherapy combined with total nephrectomy, ifosfamide, cisplatin and carboplatin were risk factors as well. Even the sole fact of having renal tumor treatment increased the odds ratio of decreased eGFR in comparison to a control cohort. Thus, it remains difficult to solely attribute a decreased renal function to a total nephrectomy. The whole treatment, including chemotherapy, surgery and radiotherapy, can negatively impact the renal function.

Nevertheless, a recent systematic review by Khondker et al. (2022) of 23 studies looking at the advantages of NSS, suggests NSS for uWT patients may be associated with a better kidney function and blood pressure in comparison to patients undergoing a total nephrectomy. The current evidence is low, and mean follow-up time was only 9.4 years (range 2.0 – 24.8) for 293 cases of uWT (35). Longer follow-up will allow for more conclusive answers on this matter.

The most important oncological risk of NSS is the possibly incomplete resection or positive surgical margin. In our own unilateral WT cases receiving NSS preoperatively planned with a 3D model (N = 27), there were no unexpected incomplete resections. Yet this cohort is very small, limiting direct conclusions. Incomplete resections leaves tumor cells behind in the retroperitoneal space and it is typically thought that this increases the risk of a local or regional recurrence. A positive surgical margin resulting in a local recurrence reduces the overall survival. This warrants an intensified therapeutic regimen (doxorubicin and/or radiotherapy) and strict patient selection is crucial. However, the influence of a positive surgical margin on a local recurrence is not that explicit. In 2013, Kieran et al. retrospectively assessed all bWT patients undergoing NSS in their center, including 21 patients. Out of five patients with a positive surgical margin (24%), only one patient had a local recurrence after treatment with adjuvant flank radiotherapy. The authors conclude that bWT patients with a microscopic positive margin are not at a higher risk for local recurrence. (36) The same was observed in the SIOP-2001 study. Out of 91 uWT patients treated with NSS, eight patients (9%) had a positive surgical margin treated with adequate postoperative therapy out of which one patient had a local recurrence (37). In our center, we did not see any local recurrences after a positive surgical margin. Groenendijk et al. 2021 concluded that NSS does not appear to be a prognostic factor for local recurrence, if performed by experienced surgeons and patients are carefully selected (38).

The essential underlying rationale for this low number of local recurrences after a positive surgical margin is the use of postoperative abdominal radiotherapy for all except low risk patients (39). Subsequently, this also raises the question of the influence of radiotherapy on the surgically treated remaining renal parenchyma if a surgical positive margin were to occur. Radiotherapy supposedly counteracts the positive functional benefit of NSS, which is a considerable argument against the use of NSS for nsuWT (40). As mentioned earlier, abdominal radiotherapy in combination with a total nephrectomy is a risk factor for a decreased eGFR in childhood cancer survivors (33). However, this is most likely related to the given radiotherapy dosage and of course the total nephrectomy. The Pediatric

Normal Tissue Effects in the Clinic (PENTEC) task force recently described the risk of renal toxicity after radiotherapy on the total kidney volume (41). Based on their review, they conclude that the risk of chronic or severe toxicity to the kidney is low (<5%) if the cumulative dose on the total volume of the kidney remains under 11 Gy in 7 fractions. This dosage is the standard of care for patients with a positive surgical margin. This risk of renal toxicity increases if nephrotoxic chemotherapeutics are given (Carboplatin, Cisplatin or Ifosfamide), but these are not regularly prescribed to nonsyndromic unilateral patients. Thus, the decrease in renal function of the spared kidney is limited. Patients may only suffer from a mildly decreased GFR of this affected kidney, with a normally functioning kidney on the contralateral side. Looking specifically at kidney function, radiotherapy seems not to counteract the positive effect of NSS for usWT patients. However, it is necessary to mention that despite a low burden of <11 Gy of radiotherapy on remaining renal parenchyma, a positive surgical margin and therewith radiotherapy should always be avoided due to the inherent risk of secondary malignancies, other radiotherapy related complications and significantly increased therapeutic burden for the patient (33,42,43). To mitigate the risk of upstaging and radiotherapy, NSS should only be considered in properly specific selected cases.

Larger prospective studies are required to fully understand the advantage of expanding the use of NSS for selected uWT patients by experienced surgeons. The consensus statements of our Delphi study can be used as the surgical assessment guideline for patient selection in the future. In these proposed studies, we can weigh the potential advantage with the possible oncological risk of NSS. The oncological consequences of this changed surgical rationale will become clear after 5 years. The systematic review on this topic by Khondker et al. also stress the importance of studying the role of different confounders (chemotherapy, radiotherapy, genetics and pathology) on surgical outcomes (35). Unfortunately, the true long-term consequence on renal function might only become clear in late adulthood, decades later (44). Besides, these consensus-based statements should first be validated on a large retrospective imaging dataset (possibly a single center PMC cohort or multi center SIOP-2001) to determine a baseline percentage of nsuWT children eligible for NSS. This may be combined with recommendations from our own single center retrospective surgical outcome study (Chapter 8). This validation is required for implementation of guidelines in an actual study protocol and should be performed together with the surgical panel of the SIOP-RTSG, to ensure utilization in agreement with oncologic principles.

9.3 FUTURE RECOMMENDATIONS FOR 3D TECHNOLOGY IN PEDIATRIC ONCOLOGIC SURGERY

Three different directions are recommended to improve the use of 3D technology across the entire field of pediatric oncologic surgery. These directions should focus on collaboration on a local, national, and international level. These recommendations are not solely based on this work but also on personal experience and data outside of the scope of this thesis.

On a local level, our efforts on implementation of 3D technology have primarily been clinically driven but implemented in research. While this allowed us to experiment and innovate, it also positions 3D technology in fixed projects and on a case-to-case basis. Moreover, our 3D technology research has been initiated on the topic of renal tumors, while there is further clinical potential of this technology for surgery of neuroblastoma, Ewing sarcoma, osteosarcoma, and different locations of yolk sac tumors. We should collaborate with multiple disciplines in our center to overcome to further expand the application of 3D technology. This can be coordinated by a clinical and scientific 3D working group or "3DLab". This working group should be positioned within the department of pediatric surgery, but work should not be limited to this department to allow for collaboration with other departments such as oncology, orthopedic surgery, neurosurgery, and maxillofacial surgery.

In care, work should focus on the expansion of 3D models for the preoperative planning of different surgical procedures. To facilitate this expansion and take 3D modelling out of research, we need to improve our quality and work processes in line with current regulations set in de Medical Device Regulation. These models should be developed by trained personal (e.g. technical physicians) and with medically CE-certified software (e.g. Materialise Mimics Innovation Suite). For each surgical procedure there should be standard operation procedures or programmed semi-automated segmentation workflow to ensure consistency and quality. Secondly, the clinical 3D working group should be responsible for the safe introduction of 3D technology, specifically for navigated surgery. They should be responsible for taking navigation research from bench to bedside, ensuring systematic use and sustainable implementation of the technology.

Finally, when we develop 3D models for preoperative planning, we can also create 3D prints to inform children and parents with a tangible model of their disease. A 3D model is an intuitive and easy to understand visualization of cancer types, making it very suitable for children. In the past we have informed a small number of patients and

children on the surgical procedure with a 3D model. The children reacted unanimously enthusiastic, and children often wanted to take the 3D models home to show to their peers. This could be further expanded within care as a service. It may also be interesting to study how 3D models influence the understanding of disease in children. This has been studied in adults, but not much is known in children. Such studies should be conducted in collaboration with the supportive care research departments to ensure appropriate scientific implementation. This should be a distinct clinical research priority and is a major recommendation.

In addition to these implementations of 3D technology in general care, there are minor recommendations. In research, we should focus on two major topics: workflow improvements with AI segmentations and intraoperative navigation technology. By choosing these two topics, we deliberately choose to not focus on preoperative imaging and planning techniques. The topic of artificial intelligence driven automated segmentation allows for observer independent, high fidelity, consistent 3D models across all type of pediatric oncologic diseases (45). This improves speed and reliability of our 3D modelling workflows which is still part of the current workflow described in 2.8. It requires a fast amount of data and due to the small number of patients in this field, data can be very difficult to obtain. However, considering the size and research facilities of the Princess Máxima Center, we have the unique opportunity to gather enough data and develop algorithms to advance in this field. Further developments in this field contribute significantly to 3D technology, by improving the fidelity of our models and allowing for implementation of the technology in more international centers.

Research on intraoperative navigation has the most direct clinical impact across the different surgical subfields. This clinical impact will persist if we follow the development strategy in earlier work. All earlier developments with surgical navigation arose from a clinical dilemma. While there are many technical solutions, designing a solution specific to a clinical pediatric problem ensured that our technical design choices were coordinated with the user and worked for our surgeons. The clinical pediatric problem and the intraoperative context should always be in the back of our minds going forward in technology development. In the broader field we have worked with multiple techniques for different surgical navigation problems, each relying on some form of guidance, for instance augmented reality, electromagnetic tracking, optical tracking, bone cutting guides or fluorescent illumination. 3D modelling is at the start of most of these guidance

techniques, stressing the importance of segmentation research for consistent quality and reliable results.

On a local level, we should first improve our workflow standardization through programming. This combines segmentation software with automated preoperative 3D surgical planning. Together they speed up and standardize the preparation for surgical navigation techniques to ensure consistent, observer independent and reliable planning. Moreover, this can allow us to further improve the volume estimation of functional renal parenchyma described in Chapter 5, which still relies on manual input from the surgeon.

On a national level, we aim to further define and formalize our current collaborations in research on intraoperative navigation. For augmented reality guided navigation, post-incision registration of AR guidance might be a major advantage for NSS in comparison to current visualization techniques and should be the further focus of research (final work package described in Chapter 7). Moreover, further developments of post-incision navigation should focus on deformable holograms to improve abdominal guidance. In most abdominal oncologic surgeries, complete resections are crucial for optimal survival of patients but there is no guidance with an intraoperative plan. Therefore, surgeons currently rely solely on a rigid model based on the preoperative plan. The development of deformable holograms with intraoperative registration and tracking (e.g. with infrared markers) can overcome this incorrect positioning of the model due to movement. This technique might help the surgeons to intraoperatively reaffirm their surgical plan, ensuring more complete tumor resections.

We have recently started a project to implement electromagnetic surgical navigation in pediatric oncologic surgery for Ewing sarcoma. The surgery department of the NKI-AVL has already implemented this technique for adult oncologic surgery, showing promising results (46,47). Redeveloping this technique towards use in children might make it very well suited for pediatric retroperitoneal tumors such as renal tumors as it allows for fast tracking of the organ. With accurate electromagnetic navigation we can translate this preoperative model to the intraoperative situation to give a more accurate estimation of the tumor margin depicted by the surgeon. This should allow to surgeon to determine the risks during the resection more intuitively.

On an international level, further developments should focus on international collaboration on larger clinical studies. As mentioned in the first paragraph of this chapter, these studies are not possible without international collaboration with leading centers in the field of pediatric oncologic surgery and 3D technology. Only with other centers

will we be able to start randomized control trials to study the clinical advantage of 3D technology in pediatric NSS. These trials should be led by one department for technical support, by whom the 3D imaging is prepared and shared with the collaborating centers. This assures consistent quality of the technology but also allows for widespread use in this narrow clinical field. International collaboration can help us to further define technological research within pediatric oncologic surgery. By sharing research aims and allocating research routes together, we create an open research environment in which resources such as data are scare. We will be able to share required data, develop new AI-based segmentation techniques, work on workflow automation and perform clinical studies without being competitors but collaborators instead.

On a global level, it is time to focus international research more on surgery. In recent years, international collaborations have led to significant developments in the field of chemotherapy (48–50), radiotherapy (51,52) and biology (53). With the start of harmonization of surgical assessments in Chapter 2, the time is right to take international surgical research further and work together on significant developments in our field.

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Dutch summary

In Nederland krijgen ongeveer 30 kinderen per jaar nierkanker. Bij een groot deel van de patiënten wordt de hele nier met de tumor chirurgisch verwijderd (Totale Nefrectomie, TN). Bij het andere deel van de patiënten wordt de tumor uit de nier verwijderd (Niersparende Chirurgie, NSS). NSS wordt gedaan bij kinderen met beiderzijdse tumoren of kinderen met specifieke overgroeisyndromen. NSS wordt alleen onder zeer strenge voorwaarden verricht bij kinderen die een enkelzijdige tumor hebben en geen overgroeisyndromen. Dit komt omdat NSS erg moeilijk is, de tumor wordt niet totaal wordt in 13,3 tot 36,4% van de operaties. Desondanks heeft NSS wel verwachte voordelen ten opzichte van TN. Zo zou de kans op chronische nierziekte op latere leeftijd verminderd kunnen worden.

In dit proefschrift hebben we onderzoek gedaan om NSS vaker mogelijk te kunnen maken voor deze specifieke patiëntengroep. Eerst hebben we gekeken welke patiënten in deze groep chirurgisch in aanmerking zouden kunnen komen voor NSS. Er zijn oncologische richtlijnen voor deze beslissing, maar er zijn nog geen chirurgische richtlijnen. Daarom hebben wij een internationale Delphi consensus studie gedaan onder experts op het gebied van NSS. Het andere onderdeel is technische verbetering op het gebied van NSS. Hiervoor hebben we 3D technologie ontwikkeld en geïmplementeerd in onze chirurgische zorg. Met behulp van 3D modellen kan een chirurg zich voorbereiden op een operatie en krijgt de chirurg een beter beeld van de anatomische relaties van de tumor van een patiënt. Daarnaast hebben wij ook gewerkt aan chirurgische navigatie met behulp van een holografisch 3D model. Het 3D model wordt holografisch in een patiënt geprojecteerd. Dit zou het vinden van de tumor makkelijker moeten maken, en de diepteperceptie van de chirurg kunnen verbeteren.

Volgend uit deze twee onderzoeksrichtingen heb ik gekeken naar de impact van 3D modellen op de chirurgische uitkomst bij patiënten die NSS hebben ondergaan in het Princes Máxima Centrum. We zagen een afname van onverwachte incomplete verwijdering van de tumor bij operaties waarbij de chirurg een 3D model heeft gebruikt tijdens de voorbereiding.

Samenvattend, wij hebben stappen gezet om de chirurgische besluitvorming en chirurgische technieken te verbeteren voor kinderen met niertumoren waarvoor niersparende chirurgie mogelijk zou kunnen zijn.

English summary

In the Netherlands, approximately 30 children per year are diagnosed with kidney cancer. For most patients, the entire kidney along with the tumor is surgically removed (Total Nephrectomy, TN). For the other patients, the tumor is removed from the kidney (Nephron-Sparing Surgery, NSS). NSS is performed on children with bilateral tumors or children with specific overgrowth syndromes. NSS is only performed under very strict conditions in children who have a unilateral tumor and no overgrowth syndromes. This is because NSS is very challenging, and the tumor is not completely removed in 13.3% to 36.4% of the surgeries. Despite this, NSS is expected to have benefits compared to TN. For instance, the likelihood of chronic kidney disease later in life could be reduced.

In this dissertation, we conducted research to make NSS more feasible for this specific patient group. First, we examined which patients in this group could be eligible for NSS surgically. There are oncological guidelines for this decision, but no surgical guidelines exist yet. Therefore, we conducted an international Delphi consensus study among experts in the field of NSS. The other part of our study focused on technical improvements in NSS. For this, we developed and implemented 3D technology in our surgical care. Using 3D models, a surgeon can prepare for an operation and gain a better understanding of the anatomical relationships of a patient's tumor. Additionally, we worked on surgical navigation using a holographic 3D model. The 3D model is projected holographically into a patient. This should make it easier to locate the tumor and improve the surgeon's depth perception.

Following these two research directions, I looked at the impact of 3D models on surgical outcomes for patients who underwent NSS at the Princess Máxima Center. We observed a trend in decreased unexpected incomplete tumor removal in surgeries where the surgeon used a 3D model during preparation.

In summary, we have taken steps to improve surgical decision-making and techniques for children with kidney tumors where nephron-sparing surgery could be possible.

Scientific contributions

Publications

1 Fitski, M., Meulstee, J. W., Littooij, A. S., van de Ven, C. P., van der Steeg, A. F., & Wijnen, M. H. (2020) MRI Based 3-D imensional Visualization Workflow for the Preoperative Planning of Nephron-Sparing Surgery in Wilms' Tumor Surgery: A Pilot Study. *Journal of Healthcare Engineering.*

2 van der Zee, J. M., **Fitski, M.**, Simonis, F. F., van de Ven, C. P., Klijn, A. J., Wijnen, M. H., & van der Steeg, A. F. (2022) Virtual Resection: A New Tool for Preparing for Nephron-Sparing Surgery in Wilms Tumor Patients. *Current Oncology*.

3 Fitski, M., van de Ven, C. P., Hulsker, C. C., Bökkerink, G. M., Terwisscha van Scheltinga, C. E., van den Heuvel-Eibrink, M. M., Mavinkurve-Groothuis, A. M., van Grotel, M., Wijnen, M. H., Klijn, A. J. & van der Steeg, A. F. (2022) Patient-specific hydrogel phantoms for the preoperative simulation of nephron-sparing surgery in Wilms' tumor patients: a feasibility study. *Annals of 3D Printed Medicine.*

4 Spijkerboer, K. G., **Fitski, M.**, Siepel, F. J., van de Ven, C. P., & van der Steeg, A. F. (2022) Augmented reality-guided localization of a chest wall tumor in a pediatric patient. *European Journal of Cancer*.

5 Van der Beek, J. N.*, **Fitski, M.***, de Krijger, R. R., Wijnen, M. H., van den Heuvel-Eibrink, M. M., Vermeulen, M. A., van der Steeg, A. F. & Littooij, A. S. (2022) Direct correlation of MRI with histopathology in pediatric renal tumors through the use of a patient-specific 3D-printed cutting guide: a feasibility study. *Pediatric Radiology*. * Acknowledged as combined first author

6 Buser, M.A.D., van der Steeg, A.F., Wijnen, M.H., **Fitski, M.**, van Tinteren, H., van den Heuvel-Eibrink, M.M., Littooij, A.S. & van der Velden, B.H. (2023) Radiologic versus Segmentation Measurements to Quantify Wilms Tumor Volume on MRI in Pediatric Patients. *Cancers*.

7 van der Zee, J. M., **Fitski, M.**, van de Sande, M. A., Buser, M. A., Hiep, M. A., Terwisscha van Scheltinga, C. E., Hulsker, C. C., van den Bosch, C. H., van de Ven, C. P., van der Heijden, L., Bökkerink, G. M., Wijnen, M. H., Siepel, F. J. & van der Steeg, A. F. (2023) Tracked Ultrasound Registration for Intraoperative Navigation during Pediatric Bone Tumor Resections with Soft Tissue Components: A Porcine Cadaver Study. *International Journal of Computer Assisted Radiology and Surgery.*

8 Wijnen, M. H., **Fitski, M.** & van der Steeg, A. F. (2023) Innovaties in de kinderoncologische chirurgie. *Nederlands Tijdschrift voor Oncologie.*

9 van der Woude, R., **Fitski, M.**, van der Zee, J. M., van de Ven, C. P., Bökkerink, G. M., Wijnen, M. H., Meulstee, J. W., van Doormaal, T. P., Siepel, F. J. & van der Steeg, A. F. (2024) Clinical Application and Further Development of Augmented Reality Guidance for the Surgical Localization of Pediatric Chest Wall Tumors. *Journal of Pediatric Surgery.*

10 Simons, D. C., Buser, M. A., **Fitski, M.**, van de Ven, C. P., ten Haken, B., Wijnen, M. H., Tan, C. O. & van der Steeg, A. F. (2024) Multi-modal 3-Dimensional Visualization of Pediatric Neuroblastoma: Aiding surgical Planning Beyond Anatomical Information. *Journal of Pediatric Surgery.*

Conference contributions

1 **Fitski, M.**, Meulstee, J. W., Littooij, A. S., van de Ven, C. P., van der Steeg, A. F., & Wijnen, M. H. (2021, June 23-27). MRI Based 3-Dimensional Visualization Workflow for the Preoperative Planning of Nephron-Sparing Surgery in Wilms' Tumor Patients [Conference presentation]. CARS 2020, Virtual Congress, Munich, Germany.

2 Eyck, Q. D., **Fitski, M.**, van der Steeg, A. F. & Wijnen, M. H. (2021, June 21-25). Towards holographic navigation for paediatric nephron sparing wilms tumor surgery: a technical feasibility study [Conference presentation]. CARS 2021, Munich, Germany.

3 Fitski, M., Van der Beek, J. N., de Krijger, R. R., Wijnen, M. H., van den Heuvel-Eibrink, M. M., Littooij, A. S. & van der Steeg, A. F. (2021, September 21-24) Direct correlation of MRI with histopathology in pediatric renal tumors through the use of a patient-specific 3D-printed cutting guide: a pilot study [Conference presentation]. SIOP 2021, Virtual Congress.

4 Fitski, M., Bökkerink, G. M., Wijnen, M. H., van de Ven, C. P., Littooij, A. S., Klijn, A. J. & van der Steeg, A. F. (2022, September 28 – October 1). Non-Contrast MRA as non-invasive vasculature imaging for pediatric renal tumor surgery, a pediatric surgical perspective [Conference presentation]. SIOP 2022, Barcelona, Spain. **Shared best poster.**

5 Buser, M. A. D., van der Steeg, A. F., Wijnen, M. H., **Fitski, M.**, van den Nieuwenhof, H. B., van den Heuvel-Eibrink, M. M., Littooij, A. S. & van der Velden, B. H. (2022 September 28 – October 1) How to accurately measure volumes in Wilms tumors on MRI [Conference presentation]. SIOP 2022, Barcelona, Spain. **Shared best poster.**

6 van der Zee, J. M., **Fitski, M.**, van de Ven, C. P., Klijn, A. J., Wijnen, M. H., & van der Steeg, A. F. (2022, September 28 – October 1). Virtual Resection: A New Tool for Preparing for Nephron-Sparing Surgery in Wilms Tumor Patients [Conference presentation]. SIOP 2022, Barcelona, Spain.

7 Fitski, M., Bökkerink, G. M., Davidoff, A. M., Murphy, A. J., Abdelhafeez, A. H., Krauel, L., Fuchs, J., Pachl, M., de Campos Vieira Abib, S., Fernandez-Pineda, I., Sarnacki, S., van de Ven, C. P., Wijnen, M. H., Klijn, A. J., Godziński, J., & van der Steeg A. F. (2023, October 11 – October 14). Nephron-sparing surgery for patients with Wilms' tumors, a surgical Delphi study consensus statement [Conference presentation]. SIOP 2023, Ottawa, Canada. **Best of IPSO session.**

PhD portfolio

Name	Matthijs Fitski
Period	2019-2024
Promotors	Prof. dr. M.H.W.A. Wijnen
	Prof. dr. M.M. Van den Heuvel-Eibrink
Copromotors	Dr. A.F.W. Van der Steeg
	Dr. A.S. Littooij

PhD Training	Year
Courses	
Supervision of Master's students, GSLS, Utrecht University	2021
Giving effective presentations, GSLS, Utrecht University	2021
Achieving your goals and performing more successfully, GSLS, Utrecht University	2021
Adobe Illustrator, GSLS, Utrecht University	2021
Intellectual Property, Paul Janssen Futurelab Leiden	2021
Basic course Regulation and Organization for Clinical Investigators (BROK), NFU	2021
Academic writing in English, GSLS, Utrecht University	2020
Research planning and time management, GSLS, Utrecht University	2020
Seminars and workshops	
IPSO Educational day	2020-2024
Research meetings Groep Wijnen, fortnightly	2020-2024
Research retreat Princess Máxima Center	2020-2023
Research meeting Princess Máxima Center, weekly	2020-2024
MICCAI Conference, Vancouver, Canada	2023
SIOP-RTSG Annual Meeting, Sevilla, Poland	2022
"Medical Imaging in Oncology" Symposium (UMCU, ISI)	2022

PhD Training	Year
Conferences	
Oral presentations	
55th SIOP Congress, Ottawa, Canada	2023
SIOP-RTSG Annual Meeting, Wroclaw, Poland	2023
36th CARS conference, Munich, Germany	2022
53th SIOP Congress, Honolulu, US (Virtual)	2021
34th CARS conference, Munich, Germany	2021
Poster presentations	
54th SIOP Congress, Barcelona, Spain	2022
52th SIOP Congress, Ottawa, Canada (Virtual)	2020
Teaching activities	
Supervising graduation internship Technical Medicine (PMC, Pediatric Surgery)	2023
Supervising graduation internship Technical Medicine (PMC, Pediatric Surgery)	2023
Supervising graduation internship Technical Medicine (PMC, Pediatric Surgery)	2022
Supervising graduation internship Technical Medicine (PMC, Pediatric Surgery)	2021
Supervising graduation internship Technical Medicine (PMC, Pediatric Surgery)	2020
Supervising clinical internships Technical Medicine (PMC, Pediatric Surgery)	2020-2024
Other activities	
Organization committee "Medical Imaging in Oncology" Symposium (UMCU, ISI)	2022
Organization committee "Medical Imaging in Pediatric Oncology" Symposium (PMC)	2021
Organization Research meeting Groep Wijnen	2020-2024
Awards	
Nominated Best of IPSO, SIOP Congress Ottawa, Canada	2023
KWF Grant 14714 2022-3 DEV accepted	2023
Shared best poster IPSO, SIOP Congress Barcelona, Spain	2022

Authorship statement

Chapter 1

The general scientific topic and direction were proposed by my promotor. I distinguished specific topics within this direction for further focus. The idea and set-up of the general introduction were mine. I delineated the overall research aim, described current literature, introduce the technology and the potential clinical impact. I revised the text two times, after comments of my supervisors.

Chapter 2

I designed and performed the Delphi study. Moreover, I determined the overall research aim, described current literature, analyzed the results and described the potential clinical impact. I wrote and revised the manuscript, after comments of my supervisors and co-authors.

Chapter 3

I have developed the workflow behind the described technology, implemented the new sequence in collaboration with the radiology department, performed the patient inclusion, coordinated the preoperative planning, conducted the data analysis, wrote the first draft of the manuscript and implemented the contributions of the co-authors and reviewers for the final publication.

Chapter 4

I designed the study, performed the data collection and management, did the patient inclusion, performed the statistical analysis together with a statistician after writing the code myself, wrote the first draft of the manuscript, implemented the contributions of the co-authors and reviewers for the final publication.

Chapter 5

I designed the study, defined the research question, performed the initial data collection for the retrospective study and proposed the methodology. The MSc student (J. van der Zee) developed the technical workflow and performed the experiments under my supervision. The student wrote the first draft and I revised it thoroughly. Afterwards the student implemented contributions of co-authors and reviewers for final publication.

Chapter 6

I designed the study concept, developed the technology, performed the patient inclusion, coordinated the simulation surgery, wrote the first draft of the manuscript, and implemented the contributions of the co-authors and reviewers for the final publication.

Chapter 7

I designed the grant proposal, designed the proposed study, wrote the proposal, and consulted all necessary internal commissions prior to submission. I submitted the proposal, and this was accepted by the Dutch Cancer Society.

Chapter 8

I performed the data collection and management, performed the analysis together, wrote the first draft of the manuscript, implemented the contributions of the co-authors and reviewers for the final publication.

Chapter 9

I wrote the first draft of the discussion after discussion with my supervisors on subjects and arguments to be included. I had the idea and set-up of the general discussion beforehand. During the whole process I asked for and implemented input from my supervisors. The general discussion represents my opinion and view which may differ from that of my supervisors.

Dankwoord

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Curriculum Vitae

Matthijs Fitski was born on the 19th of June, 1993 in Utrecht, The Netherlands. He was raised in Maarssen and went to high school in Breukelen, the RSG Broklede. After six years, he passed his VWO in June 2012. In September 2012, he continued his career by starting with the bachelors degree Technische Geneeskunde at the University of Twente in Enschede. In July 2016, he finished his bachelors degree.

Matthijs continued with his masters degree Technical Medicine at the University of Twente and followed the track Medical Imaging and Interventions. As a part of this master track, he obtained a degree for Radiation Expertise level III. Moreover, he performed four 10-week internships at the UMC Utrecht (department of Orthopedics), Antoni van Leeuwenhoek (department of Radiology), AmsterdamUMC (department of Radiotherapy) and the Princess Máxima Center for Pediatric Oncology (department of Pediatric Surgery). At the latter, he also performed his year long graduation internship.

After graduating from Technical Medicine in September 2019, Matthijs started as a PhD-student at the department of Pediatric Surgery in the Princess Máxima Center for Pediatric Oncology in October 2019. Here he performed pre-clinical and clinical research on the use of 3D visualization technology in the field of pediatric oncologic surgery. His research was performed under the supervision of prof. dr. M.H.W.A. Wijnen, prof. dr. M.M. van den Heuvel-Eibrink, dr. A.F.W. van der Steeg and dr. A.S. Littooij. During his PhD, Matthijs has performed research within but also outside the scope of his PhD with many different departments. As of August 2024, Matthijs continues to work at the Princess Máxima Center for Pediatric Oncology, where he will continue his research and join the medical staff of the department of Pediatric Surgery, to further work on the implementation of 3D technology in the hospital together with the 3DLab of the UMC Utrecht.