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Vascular Access

A decision tree to guide long term venous access placement in children and adolescents undergoing surgery for renal tumors☆,☆☆,★,★★,☆☆☆

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ABSTRACT

Background/Purpose: While many children with renal tumors require long term venous access (VA) for adjuvant chemotherapy, certainly not all do. This study develops and tests a VA decision tree (DT) to direct the placement of VA in patients with renal tumors.
Methods: Utilizing data readily available at surgery a VADT was developed. The VADT was tested retrospectively by 2 independent reviewers on a historic cohort. The ability of the VADT to appropriately select which patients would benefit from VA placement was tested.
Results: 160 patients underwent renal tumor surgery between 2005 and 2018. 70 (43.8%) patients met study criteria with median age of 45.1 months (range 1.1–224); 73% required VA. Using the VADT, VA placement was "needed" in 67.1% of patients and "deferred" in 32.9%. Interrater reliability was very high (kappa = 0.97, 95% CI 0.91–1, $p < 0.001$). The sensitivity and specificity of the VADT to correctly decide on VA placement were 0.92 (0.8–0.98) and 1 (0.79–1). Using the VADT, no patient would have undergone unnecessary VA placement. In reality, 4.3% of patients had an unnecessary VA placed which required a subsequent removal.
Conclusions: These preliminary data support the continued study of this VADT to guide intraoperative decisions regarding VA placement in patients with renal tumors.
Level of evidence: III — Study of diagnostic test.

Children and adolescents with renal tumors often require adjuvant chemotherapy. As survival for these patients has improved dramatically through cooperative group study [1], current investigational priorities are focused on quality improvement and safety with a goal of reduction in treatment-related morbidity [2]. Within that aim, there are important issues of care outside of direct oncologic surgical or medical treatment (i.e. prior to, during and after therapy) that can affect long-term morbidity. For example, while there is a relatively low risk-to-benefit ratio for diagnostic imaging in the detection of a potential malignancy, a recent study has identified opportunities to decrease radiation exposure during initial imaging workup and staging for patients with renal tumors [3]. Other work has shown that early feeding postoperatively and the avoidance of routine bowel prep or nasogastric tube decompression are associated with a shorter time to discharge [4].

Optimally, surgical care can be consolidated so that all necessary interventions are performed at one time, specifically extirpation and long term venous access (VA) placement. Despite the conflicting evidence about age and anesthesia exposure and neural development [5–8], consolidation of procedures to minimize anesthetic exposure is appealing for patient convenience as well as from a cost and convenience perspective. While the majority of patients with renal tumors require long term venous access for adjuvant chemotherapy, certainly not all do. Thus, placing VA in all patients represents unnecessary risk exposure and identification of patients who will truly require VA would be fruitful. This study develops and tests a VA decision tree (DT) which accounts for available pre- and intraoperative factors to direct the placement of VA in patients with renal tumors. The study hypothesis is that this VADT will minimize the chance that a patient will have and unnecessary VA placed.

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1. Materials & methods

1.1. VADT development & definitions

The VADT was developed with consensus expert review and pilot testing by three expert renal tumor surgeons. The DT was developed considering factors readily available at the time of surgery (age, imaging, tumor characteristics, and frozen section) that may predict a patient's need for adjuvant therapy according to COG protocols. For example, RCC is most likely with patient age > 12 years [9] and the very low risk Wilms tumor protocol identifies specific factors whereby adjuvant chemotherapy may be completely eliminated, i.e. age < 2 years and tumor weight < 550 g [10,11]. Thus these factors were included in the VADT. Intraoperative frozen section to differentiate between Wilms from non-Wilms tumor, or benign vs. malignant diagnoses has previously demonstrated adequate agreement with final pathologic diagnosis in pediatric renal tumors [12]. The developed VADT is shown in Figs. 1 and 1b, with frozen section results in Fig. 1b.

A *false positive* was defined as placement of VA when the VA was not ultimately needed based on the clinical scenario. Such a false positive exposes patients to an unnecessary procedure for VA placement and associated risks, and necessitates a subsequent operation to remove unnecessary VA. A *false negative* was defined as deferral of VA placement when it was actually needed based on the specific clinical scenario. This would necessitate another operation to place VA. The a priori goal of utilizing the VADT was to minimize the number of false positives

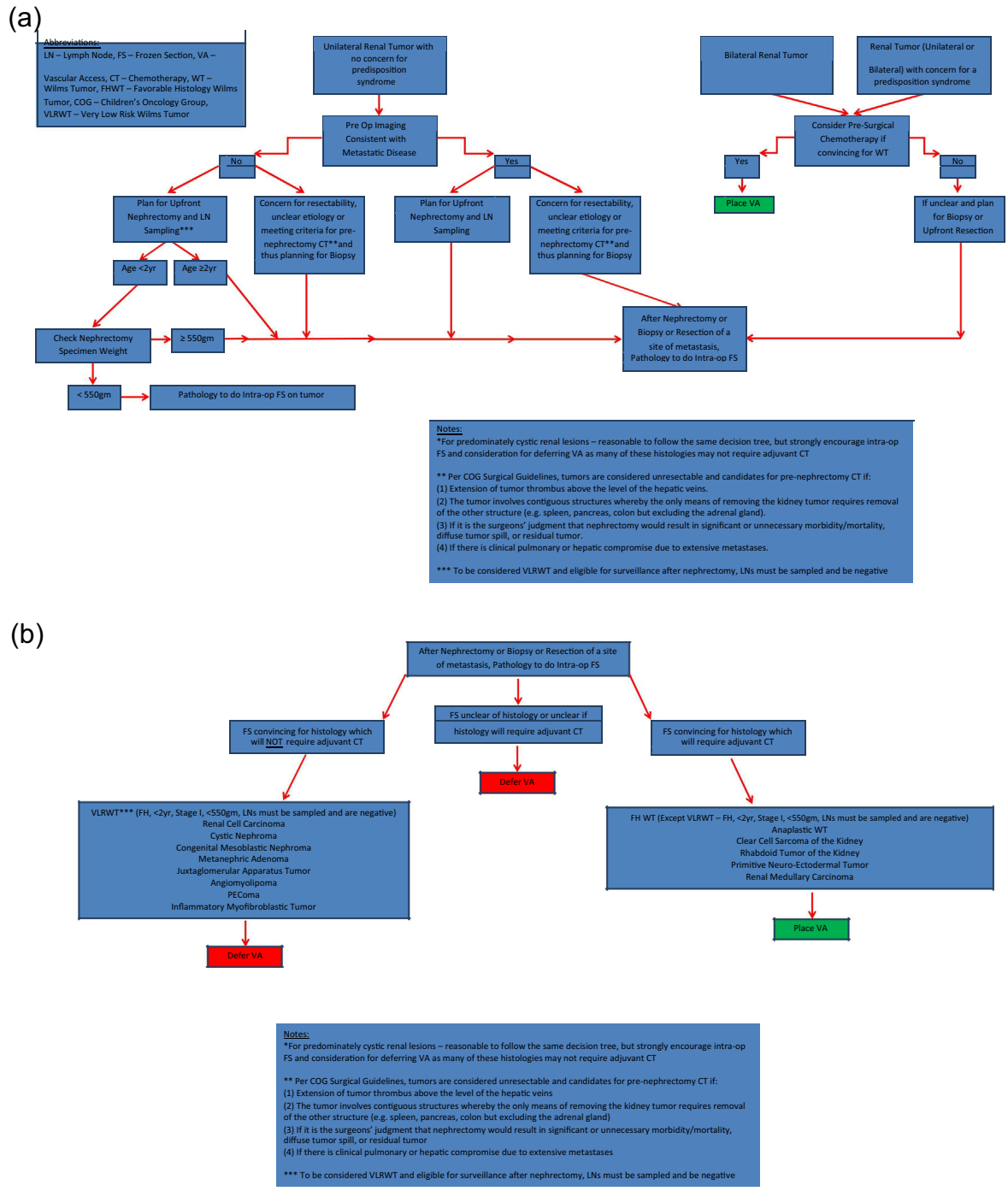

Fig. 1. (a) Preoperative factors for the proposed VADT; (b) Frozen section factors for the proposed.

(unnecessary VA placement), thus accepting a possibility that the patient may need a return trip to the operating room for VA placement. While the initiation of adjuvant chemotherapy, if necessary, is generally recommended 2 weeks after nephrectomy, this is typically more than enough time for pathology to settle on a definitive diagnosis, oncology to determine a plan with respect to adjuvant therapy, and VAD to be placed should it ultimately be needed. Thus the VADT was developed to avoid unnecessary placements over accurately identifying who would definitely need long-term VA.

1.2. Study population

Patients who underwent surgery for a real tumor were identified between 2005 and 2018. Inclusion criteria were patients 0–18 years undergoing surgery for a renal mass suspicious for malignancy. Specifically, this could include VA placement alone, biopsy, or radical or partial nephrectomy. The study exclusion criteria included patients undergoing nephrectomy, partial nephrectomy or renal biopsy for nontumor indications. Also, if during the DT analysis, frozen section pathology data would have been used, patients were excluded from the review if no frozen section data were available.

The VADT was tested using only the clinical information that would have been available to the surgeon at the time of surgery. This testing was done retrospectively on a case-by-case basis by 2 independent reviewers (AC, BTW). Reviewers were blinded to final pathology, if VA was placed or not, and if VA was required for adjuvant therapy or not. Reviewers were given access to pre- and intraoperative information only and asked to apply the VADT to determine if VA should be placed or not at the time of extirpation. A final recommendation of *place VA* or *defer VA* was given by each reviewer. Discrepancies between the reviewers were resolved by consensus review with the senior author.

1.3. Data analysis

The interrater reliability (agreement between reviewers) using the VADT was assessed with Cohen's kappa (0.61–0.80 substantial agreement, and 0.81–1 very good agreement). Specific analysis of cases where reviewers disagreed was also done to determine where the disagreement occurred.

Two broad comparisons were made to whether or not the VA was actually needed. First was the *VADT prediction*, which compared the VADT predictive outcome (place VA or defer VA) to what was needed in reality (did the patient need long term VA for adjuvant therapy or not). Second was the *reality comparison*, which compared what happened in reality (was VA placed or deferred) and what was needed in reality (did the patient need adjuvant therapy or not). The results of the VADT 3 prediction and if VA was placed in reality were then compared to each other to examine how many patients underwent additional procedures/were exposed to additional risks.

2. Theory

Identification of which patients who need concomitant VA placement at the time of initial surgery for renal tumors using the proposed VADT may decrease potential risk exposure in those who do not need VA placement.

3. Results

160 patients undergoing renal tumor surgery were identified, 70 of whom met study criteria (table 1). Based on final pathology results and the clinical scenario, 51 (73%) patients required VA placement for adjuvant therapy. Using the VADT, VA should be *placed* in 47 (67.1%) and *deferred* in 23 (32.9%). Interrater reliability of the VADT was high: $\kappa = 0.97$, 95% confidence interval (CI) 0.91–1, $p < 0.001$. There was a single case in which the reviewer disagreed, which was a stage III congenital mesoblastic nephroma (intraoperative spillage and omental implants) where the patient ultimately did receive neoadjuvant chemotherapy. There were no complications related to VA placement in any patient.

Table 2 shows the rates of VA placement and deferral, using the VADT and then what happened in reality, and the necessity of VA based on final pathology results. The ability of the VADT to correctly predict the need for VA placement was excellent, with a sensitivity = 0.92 (95% CI 0.8–0.98) and specificity = 1 (95% CI 0.79–1). The positive predictive value of the VADT was 1 (95% CI 0.91–1) and the negative predictive value was 0.826 (0.6–0.94). This compares to the intraoperative decision in reality, which had a similar sensitivity = 0.92 (95% CI 0.8–0.98) but a lower specificity = 0.84 (95% CI 0.60–0.96). The intraoperative decision made in reality when compared to what was truly needed was a positive predictive value was 0.94 (95% CI 0.82–0.98) and the negative predictive value was 0.80 (0.56–0.93).

Both when the intraoperative decision which was made in reality and if the VADT were used retrospectively, there were 4 (5.7%) false negatives (VA was deferred when needed), which required a subsequent operation for VA placement. These four patients are summarized in table 3. There were no false positives (unnecessary VA placements) with VADT; thus, no patients would have required a subsequent operation to remove unnecessary VA. In reality, 3 (4.3%) patients had VA placed which were unnecessary and required a subsequent operation for removal. Taken together, using the VADT, 4/70 patients (5.7%) would have required an additional procedure, all for VA placement. For the intraoperative decision made in reality, 7/70 patients (10%) required a second procedure (3 for unnecessary VA removal and 4 for VA placement), $p = 0.245$.

Table 1
Patient cohort demographics.

Characteristic	
n	70
Median age (months)	45.1 (range 1.1–224)
Patients with age < 24mo	22 (31.4%)
Laterality	
Bilateral	17 (24.3%)
Right	32 (45.7%)
Left	21 (30.0%)
Initial procedure performed (%)	
Biopsy	15 (21.4%)
Partial nephrectomy	11 (15.7%)
Radical nephrectomy	35 (50%)
Long term VA alone	9 (12.9%)
Intraoperative frozen section done	53 (76%)
Cohen's kappa for correlation between frozen section and final pathology	0.76 (95% CI 0.63–0.9), p-value <0.001
Final pathology	
Wilms tumor	48 (68.6%)
Renal cell carcinoma	4 (5.7%)
Congenital mesoblastic nephroma	4 (5.7%)
Cystic nephroma	4 (5.7%)
Other	3 (4.3%)
Renal medullary carcinoma	1 (1.4%)
Rhabdoid tumor	1 (1.4%)
Clear cell sarcoma	1 (1.4%)
Angiomyolipoma	1 (1.4%)
Juxtaglomerular tumor	1 (1.4%)
Metanephric adenoma	1 (1.4%)
Neuroblastoma	1 (1.4%)
VA placed at time of surgery	
VADT prediction	47 (67.1%)
Intraoperative decision made in reality	50 (71.4%)
VA removals after surgery	
VADT prediction	0 (0%)
Intraoperative decision made in reality	3 (4.3%)

Table 2
Comparison of VADT prediction and reality vs. necessity of VA based on final pathology.

	Was VA really needed?					
VADT prediction	**Yes**	**No**	**Sensitivity (95% CI)**	**Sensitivity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
Place VA	47 (67.1%)	0 (0%)	0.92	1	1	0.826
Defer VA	4 (5.7%)	19 (27.1%)	(0.80-0.98)	(0.79-1)	(0.91-1)	(0.6-0.94)
Intraoperative decision made in reality	**Yes**	**No**	**Sensitivity (95% CI)**	**Sensitivity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
VA placed	47 (67.1)	3 (4.3%)	0.92	0.842	0.94	0.8
VA deferred	4 (5.7%)	16 (22.9%)	(0.80-0.98)	(0.60-0.96)	(0.82-0.98)	(0.56-0.93)

4. Discussion

Utilizing clinical information available intraoperatively and in "real time," the proposed VADT appears to accurately predict VA placement at the time of surgery for children and adolescents with renal tumors suspicious for malignancy (sensitivity = 0.92, specificity = 1) to align with current adjuvant chemotherapy in accordance with COG protocols. The VADT appears reliable and easy to use, as evidenced by the high interrater reliability ($\kappa = 0.97$). Both using the VADT and the intraoperative decision made in reality, four patients had deferred VA at the time of extirpation and needed a subsequent operation for VA placement, so the VADT was not an improvement in avoiding additional VA placements. However, in reality, three patients had VA placed which were unnecessary, which may have been avoided if the proposed VADT had been applied. Of note, in all three of these patients, the VA was placed as the first step of the case and thus any information gained from subsequent surgery (tumor weight, frozen section histology) was inherently unable to inform the need, or lack thereof, for VA. Examples such as these, highlight that the VADT may minimize the number of unnecessary VA placements, thus decreasing exposure to unnecessary procedures and associated risks. Avoiding such unnecessary additional procedures was the study objective, and it appears to be the strength of the proposed VADT.

Long-term VA is essential to the necessary adjuvant treatment of children with cancer. However, device related complications are commonly seen in this patient population and may prompt VA device removal or replacement, prolong hospitalizations and sometimes even result in death [13]. When considering the implication of utilizing the proposed VADT, it is important to balance potential benefits versus harms. For those with VA placement deferred when it is truly needed, another operation will be necessary, which means another anesthetic and increased cost. However, when considering those who undergo VA placement when it is unnecessary, this exposes patients to unnecessary potential harm, including misplacement, pneumothorax, hemothorax, arterial puncture, hemorrhage, hematoma, cardiac tamponade, coiled catheter, arrhythmia and additional radiation exposure [13–17]. A recent review of pediatric oncology patients reported an overall 39.5% rate of Clavien–Dindo grade III and IV complications related to VA placement [13]. Overall, the authors feel that the low incidence of needing a subsequent operation to place VA utilizing this proposed VADT is worth the tradeoff of not exposing children to unnecessary risks related to VA placement and subsequent removal.

Such a selective approach to VA placement in pediatric patients with renal tumors will only increase as there are proposals from the Children's Oncology Group for expanding the role of surgery-only for those with low risk favorable histology Wilms tumor [11,18]. Current criteria for those to be considered for surgery-only include: favorable histology, age < 2 years, stage I with adequate LN sampling, no high risk genetic mutations (loss of heterozygosity), no predisposition syndromes and tumor weight < 550 g [10]. Specifically, the goal is to avoid chemotherapy-associated toxicities and complications related to VA [11]. Proposed expansion of age and tumor weight criteria would increase the number of patients potentially eligible for this treatment strategy and would make the identification of patients needing or potentially not needing VA at the same time as nephrectomy more important. The authors propose that the VADT would need to be modified in parallel to these treatment protocol changes and thus would evolve with these therapeutic changes.

The adoption of novel strategies and techniques to improve outcomes in VA placement is not new. The introduction of ultrasound guidance for internal jugular vein placement for VA has proven safer and quicker than non-image-guided access [19] and this is now considered a standard of care [20]. Additionally, perioperative radiation safety interventions during VA placement have been shown to reduce radiation exposure up to 80% in children [21]. The elimination of routine postoperative chest x-ray decreases radiation exposure without missing lung related complications in the absence of clinical symptoms [22]. Dressings and securement devices have also been studied to decrease complications and failures [23]. The addition of the proposed VADT aligns with these quality improvement measures and can minimize exposure of an unnecessary procedure in children with renal tumors who do not need VA for adjuvant chemotherapy.

Algorithms are frequently used in medicine to simplify issues and help with treatment plans across pediatric surgery, urology and oncology. Such examples include enhanced recovery pathways after surgery [24] and diagnosis and management of pyloric stenosis [25]. But beyond using frozen section pathology in determining margin positivity for tumor excision in a variety of malignancies, there are few decision trees used to guide intraoperative decision making. A recent article has highlighted that during lumpectomy for breast cancer, where the rate of positive margins at final pathology is 20%, the use of an intraoperative spectroscopic

Table 3
False negative and false positive cases.

VADT false negative cases (VA deferred when actually needed)	
Stage III CMN	VADT → defer VA Reality → deferred VA Ultimately, received VA as oncology team elected for adjuvant therapy
Metastatic RCC	VADT → defer VA Reality → deferred VA Ultimately, received VA for cytotoxic chemotherapy, which is not in line with contemporary management of pediatric RCC
VLRWT	VADT → defer VA Reality → deferred VA Ultimately, central COG pathology review found micro-metastases in the lymph nodes, thus upstage to III and received VA for adjuvant chemotherapy
NBL vs. WT on frozen section	VADT → defer VA Reality → deferred VA Ultimately, was WT on final pathology and received VA for adjuvant chemotherapy
"Reality" false positive cases (VA placed when not needed)	
RCC	VADT → defer VA Reality → VA placed
CMN	VADT → defer VA Reality → VA placed
Completely resected NBL	VADT → defer VA Reality → VA placed

CMN, congenital mesoblastic nephroma; RCC, renal cell carcinoma; VLRWT, very low risk Wilms tumor; NBL, neuroblastoma; WT, Wilms tumor; COG, Children's Oncology Group.

assessment was accurate and may allow more complete excision, thus avoiding subsequent excisions for positive margins [26]. In cardiac surgery, where there are significant alterations in coagulation, groups from Italy have proposed the Granducato algorithm to reduce blood loss and transfusion requirements intraoperatively, using real time information [27]. As medicine becomes more personalized, the identification of specific variables that can classify subgroups is attractive and becoming more commonplace [28]. While this is being extensively studied in machine learning, there are also opportunities for decision tree algorithms to be applied to real time decision making in the operating room, which is what the proposed VADT aims to accomplish.

Limitations of this study include a retrospective analysis of single institutional data, which may not be generalizable to all institutions. The VADT was designed using COG protocols, which tend to favor postoperative chemotherapy, and as such it may not be able to be extrapolated to centers using presurgical chemotherapy in line with SIOP protocols. Also, many of the cases were surgically managed by the authors who developed the VADT and likely followed a rudimentary form of the DT in their practice even before the DT was formally developed. General pediatric renal tumor knowledge and treatment protocols have changed over time, and these changes may not have been utilized clinically during the earlier years of patients included in this study. It is also unknown if there were other clinical data available intraoperatively to the surgeon that were not included in the chart or analysis that perhaps weighed into the decision to place VA or not. It would be interesting to expand this study to a wider array of abdominal tumors which may similarly be managed with upfront resection with possibility of postoperative adjuvant chemotherapy to see if similar trends are observed. Additionally, cost data were not available but will be studied in the future to determine the cost-effectiveness of this approach. The next step is to validate the VADT prospectively with a multi-institutional clinical trial and additionally, it will be necessary to modify the current VADT as pediatric renal tumor management protocols evolve to verify success with these changes. However, while future changes will need to be studied and validated, this initial study is a proof of principle that such a VADT using clinical data, available intraoperatively, in real time, can help inform the need for VA placement in children and adolescents with renal tumors.

Despite the above limitations, there are three main recommendations from the study:

1. There is no need to place long term VA at the beginning of the case in a child or adolescent who is undergoing a nephrectomy or biopsy for a renal tumor. Access should be secured only if frozen section (and specimen weight in those <2 years old) confirms the need for chemotherapy. Similarly, in most cases where a child presents with a renal mass, there is time to plan accordingly before surgery.
2. Intraoperative frozen section should be mandatory in any case that has planned concurrent VAD placement.
3. When in doubt, wait for final pathology and accept a small number of patients having a second anesthetic for port placement.

5. Conclusion

These preliminary data support that the proposed VADT can guide intraoperative decisions regarding the necessity of VA placement in children and adolescents with renal tumors. The VADT appears reliable and easy to use clinically. While it may not identify all patients who will ultimately need VA, it minimizes the probability that a patient will be exposed to risks of unnecessary VA placement and removal. Continued investigation is necessary, as well as evolution of the VADT to parallel changes in pediatric renal tumor treatment guidelines.

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