Surgical Aims

Pediatric Surgical Oncology Newsletter
Volume 1, Number 1, 2024

this issue

Introduction from the COG Surgical Discipline Chair

It is my great pleasure to introduce the inaugural edition of "Surgical Aims," the new electronic newsletter created to disseminate current information relating to pediatric surgical oncology. Specific topics will include updates on clinical trial results, opening of new protocols, summaries of presentations at relevant meetings, reviews of recent publications in the field, descriptions of new advances in surgical technology and reviews of standard-of-care disease management. It is anticipated that the newsletter will be sent out at least three times per year with additional issues coming out as more timely distribution requires. Thanks to Marcus Malek, Sara Mansfield and Joe Fusco for taking on the responsibility for putting out this newsletter, and special thanks to Ken Gow for overseeing the logistics of its preparation.

For this inaugural issue, I would like to report on the COG surgeons' retreat held in Houston this past summer. Twenty-four surgeons were able to attend (plus three who were stranded at home attended virtually). Also in attendance were Doug Hawkins, COG Chairman, Lindsay Renfro, COG statistician and other members of COG administration. Topics included greater inclusion of surgeons in COG protocol development, and the development of synoptic operative notes that can be used by all surgeons (more on this to follow in a future newsletter). In addition, ways to boost accrual to the surgery-led COG AOST2031 protocol evaluating the roles of thoracoscopy versus thoracotomy for osteosarcoma metastases (see article in this issue) were discussed. Overall, it was felt that the retreat was extremely productive. Thanks to Jed Nuchtern for hosting.

Andrew Davidoff, MD
Chair, Surgical Discipline Committee
Children's Oncology Group

Information for Upcoming COG Meetings

Traditionally, there have been two COG meetings per year, one in the spring and one in the fall. In recent years, the fall meeting has been open to all COG members, with an education focus, while the spring meeting has been a more limited attendance, "invitation-only" meeting with a "working" focus. The style of the spring meeting has just changed; this year it will have even more limited attendance, greater focus on being a working meeting with specific deliverables being anticipated and invitations to attend being distributed only by disease chairs (not disciplines, like surgery, although it is expected that disease chairs will invite some surgeons). Next year (2025), however, the spring meeting will be open to all members, but it will strictly be a virtual meeting. After this two-year experiment, this new approach to the spring meeting will be reassessed. Fall meetings will continue to be open (in person) to all members.

Additionally, for each fall meeting, the surgery discipline chair is given a limited number of "funded" slots to distribute to COG surgeons. These will preferentially be given to Young Investigators and to those for whom attending the meeting is financially difficult. Please reach out to Andrew Davidoff (Andrew.Davidoff@StJude.org) to request one of these funded slots.

Upcomging COG meeting dates:

Sept 24-27, 2024	Apr 7-11, 2025	Sept 16-19, 2025
Open, New Orleans	Open, Virtual	Open, New Orleans

Other Meetings of interest:

** May 15, 2024 **
Come one day early to APSA for the International Pediatric Surgical Oncology (IPSO) program, Phoenix, AZ

June 5-7, 2024
Renal Tumor Biology Group, New York, NY

October 17-20, 2024
International Society of Pediatric Oncology (SIOP), & International Pediatric Surgical Oncology (IPSO), Honolulu, HI

November 13-16, 2024
Connective Tissue Oncology Society (CTOS), San Diego, CA

May 25-28, 2025
Advances in Neuroblastoma Research, Washington, DC

Molecular Characterization Initiative

In a collaborative effort, the Children's Oncology Group and the National Cancer Institute have launched the Molecular Characterization Initiative (MCI) via APEC14B1 Project:EveryChild. The MCI offers paired somatic and germline DNA sequencing and an RNA fusion assay with an approximate 3 week turn around for results. Sequencing is performed for eligible patients from COG institutions without charge to the patient or your site, and your site will receive enhanced per case reimbursement for patients enrolling to the MCI. In addition to CNS tumors, the list of eligible rare tumor diagnoses is below. Eligible patients must be 25 years or younger with a newly diagnosed tumor and receiving treatment at a COG-affiliated institution.

Eligible Tumor Diagnoses:

- Soft Tissue Sarcomas
- Thyroid Carcinoma
- Colorectal Carcinoma
- Gastrointestinal Stromal Tumor
- Adrenocortical Carcinoma
- Nasopharyngeal Carcinoma
- Retinoblastoma
- Melanoma
- Desmoplastic Small Round Cell Tumor
- Pancreatoblastoma
- Neuroendocrine Tumor
- Pleuropulmonary Blastoma
- Gonadal Stromal Tumor
- Any other carcinoma

PROJECT:EVERYCHILD

MCI Contact Information:

The rare tumor committee would be happy to answer any questions or concerns at MCIRAR@childrensoncologygroup.org

More detailed study information can be found at:

https://www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative/data-ecosystem/molecular-characterization

AOST2031: Management of Pulmonary Osteosarcoma Metastases

The importance of Surgeon-Led COG Trials

AOST2031, A Phase 3 randomized control COG trial comparing open vs thoracoscopic management of pulmonary metastases in patients with osteosarcoma is open and enrolling (see visual abstract on the following page for protocol summary). The protocol has been amended to address concerns previously raised by the COG surgical community, including expanding the allowable time from CT to enrollment (to 14 days), permitting enrollment for patients with previous diagnostic biopsy, and allowing patients who recently completed chemotherapy (rather than requiring them to still be on therapy). Co-enrollment on the chemotherapy trial AOST2032 is also permitted. Tim Lautz, the study's vice chair, explains, "Enrollment remains slow, and we really need your help to make this study a success."

Pediatric surgical oncologists understand the critical surgical questions facing the children we treat. Peter Ehrlich, surgical oncologist and longtime member of the COG, explains: "The process of developing, obtaining approval, and executing a study is a lot of work. Successful clinical trials just don't happen."

In fact, COG (POG, CCSG, NWTSG and IRS) has ever only sponsored five surgeon led clinical trials. The first in the 1990's was funded to look at the utility and the efficacy of open versus thoracoscopic or laparoscopic biopsy. Unfortunately, this study was a failure, enrolling 4 children and only opening at 26 centers. However, there are some surgical success stories: NWTS-5 /ARENO532 (nephrectomy only), the Bilateral Wilms Tumor (ARENO534) study, and observation of perinatal neuroblastoma (ANBL00P2) study were successfully completed and changed the way we manage a subset of patients with Wilms tumor and neuroblastoma.

The fifth study is AOST2031. As Peter Ehrlich explains: "This study underwent rigorous development and review before it was approved. The surgical PI spent several years doing preliminary work to justify the study. For our patients this is a critical question. The answer may impact the event free survival, overall survival, quality of life and late effects. This study opened about a year ago and has been struggling to enroll children. The children exist and we are the best ones to make AOST2031 a surgical success!"

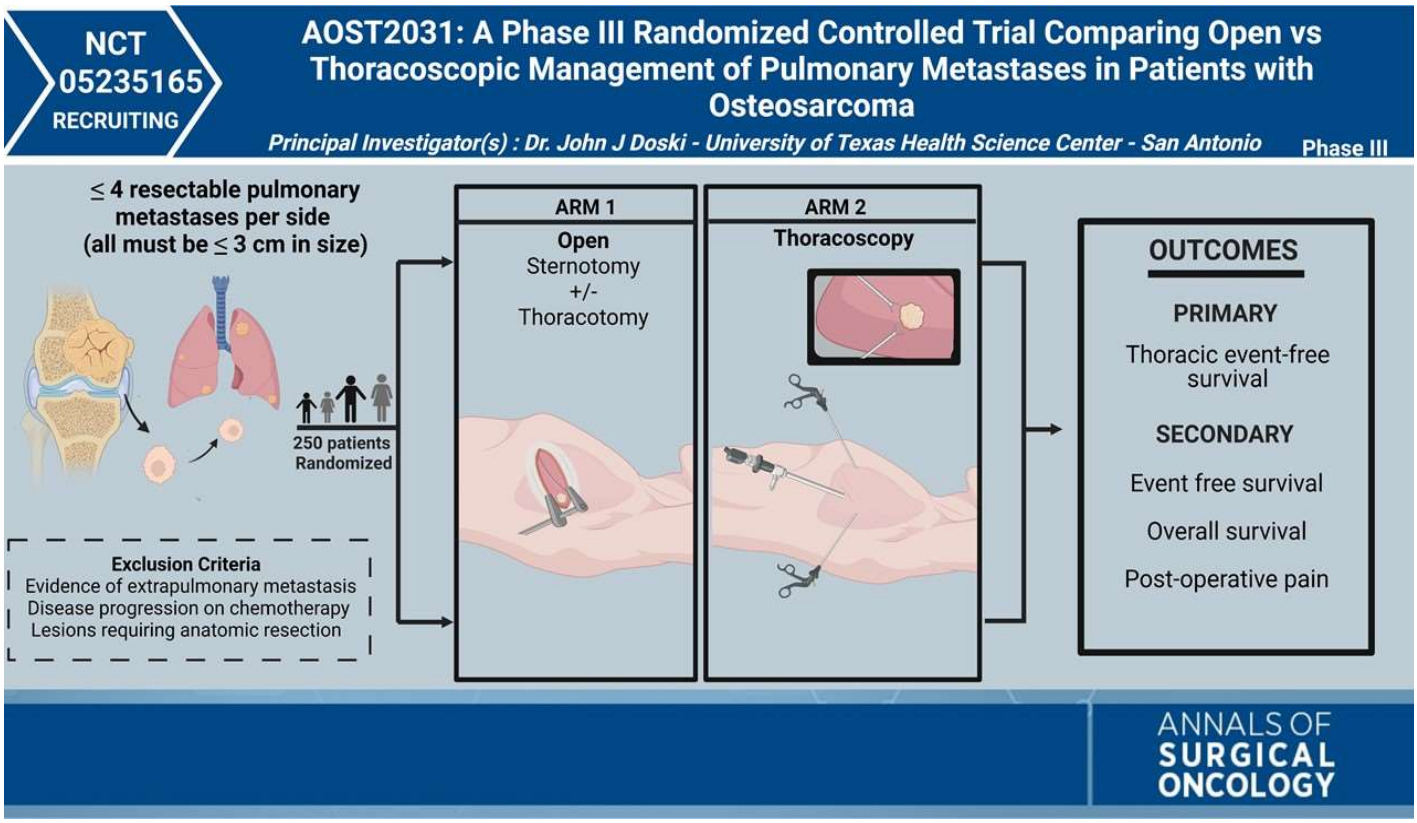
"We can make this study successful."
- Peter Ehrlich, MD

Information regarding eligibility and recent protocol ammendments are continued on the following page.

Ehrlich goes on to list several things you can do to make this study succeed:

1. Each of us at our institution needs to promote this study. Be the study champion.
2. Make sure the study is open at your institution. COG has designated this study as a priority and is using the Amazon grant money to pay institutions to get IRB approval.
3. Meet with your oncology/sarcoma team and make sure you know about every sarcoma child being treated at your institution.
4. If a child is eligible go with the oncology team to speak to the family and help with the consent. We can't expect non-surgeons to recruit for us.
5. Accept the randomization, we don't know the answer to the question!

Contributed by:
Tim Lautz & Peter Ehrlich



The above visual abstract provides a summary of inclusion and exclusion criteria. As a reminder, patients are eligible if they have oligometastatic (4 nodules or fewer per side) pulmonary disease at diagnosis or first relapse. In an effort to overcome barriers to enrollment, the study committee has enacted two amendments. The amendments are summarized in the following amendment posted on the COG website and detailed here:

https://cogmembers.org/prot/aost2031/AOST2031SurgeryStudyInfoSheet.pdf

- For patients with newly diagnosed osteosarcoma, surgery no longer must occur while still receiving chemotherapy, but can also occur within 60 days of initial chemotherapy completion (see section 3.2.3.1)
- Exclusion language clarified to rule out "chest wall" lesions rather than "pleural" lesions. (see section 3.2.6). With this new language, nodules at the very periphery of the lung, indistinguishable from visceral pleura, can be included.
- Exclusion language clarified to allow patients who had prior diagnostic lung biopsies. (Section 3.2.9 updated to only exclude patients with prior therapeutic pulmonary surgery)
- Allowed time interval from CT to enrollment increased to 14 days (still must be within 28 days of surgery, see section 3.1.4 and 3.2).
- Allowed interval between the first and second side of a staged bilateral thoracotomy increased to 8 weeks (see section 4.1)
- The permitted systemic therapy has been revised from “systemic therapy considered by the treating physician as at least equivalent to methotrexate, doxorubicin and cisplatin (MAP)” to “systemic therapy considered by the treating physician to be standard treatment for newly diagnosed osteosarcoma (eg, cisplatin-doxorubicin or ifosfamide-based drug regimens)” (see section 3.2.3.1).
- A 1-page lay language summary was added in the study consent form to help patients understand reasons why a surgeon may prefer to do an open surgery or a VATS procedure.

For questions regarding AOST2031 please contact:
Tim Lautz, MD: tlautz@luriechildrens.org
John Doski, MD: jjdoski@gmail.com

Updates from the COG Germ Cell Tumor Committee

Three notable studies have recently been reported by the Germ Cell Tumor committee. First, a recent report by Billmire et al sought to ask if preoperative imaging can be used to distinguish benign from malignant tumors and guide surgical staging in malignant nongerminomatous ovarian germ cell tumors. The authors report 133 patients, none who had purely cystic tumors. Over 80% of these malignant tumors had a mixed cystic and solid appearance, a quarter of these with calcifications. Importantly, these tumors were of mixed histology that included both mature and immature teratoma in 54% of cases, in addition to malignant histology. The authors conclude that only 13.5% of the malignant lesions were pure solid and 85% had a mixed appearance similar to what may also be found with a benign teratoma. This report shows that imaging characteristics may not differentiate benign from malignant ovarian masses and certainly should not be used to prevent complete surgical staging[1].

Additionally, Dicken et al sought to understand if frozen section could be used in pediatric and adolescent patients with ovarian germ cell tumors to guide the extent of surgical staging. The authors report 60 patients with malignant lesions with both frozen section and final paraffin section available and identified that intraoperative frozen section analysis led to an incorrect diagnosis in 38.3% of patients with 13.3% read as completely benign and 16.7% as immature teratoma only. The authors reinforced that this inaccuracy would lead to inaccurate staging in almost 40% of patients and therefore concluded that intra operative frozen section is not reliable to limit the use of surgical staging in this population. The authors hypothesize that this inaccuracy may be due to the mixed nature of ovarian germ cell tumors, often with more than one malignant histology that may lead to sampling error. Additionally, pathologists have commented that the histologic patterns for the malignant components of germ cell tumors are not as characteristic on frozen section analysis[2].

Lastly, Rich et al evaluated the role of lymphovascular invasion (LVI) in nongerminomataous ovarian germ cell tumors in an effort to assist with risk stratification in these patients as LVI is a known prognostic risk factor for testicular germ cell tumors. The authors reviewed 130 patients and identified a correlation between LVI and other poor prognostic factors including higher stage and age > 11 years. LVI was not found to be associated with EFS or OS in the intermediate risk group, and further work is necessary to determine the effect of LVI on long-term disease free survival. The authors recommend routinely incorporating LVI status into institutional pathology reports for this patient population[3].

GCT Updates provided by Barrie Rich, MD – member of the COG GCT Committee

GCT Articles of Interest Citations:

1. Billmire D, Dicken B, Rescorla F, et al. *J Ped & Adol Gynecology 2021; 34: 383-386.*
2. Dicken BJ, Billmire DF, Rich B, et al. *Gyn Onc* 2022;166:476-480.
3. Rich BS, Dicken BJ, Billmire DF, et al. *J Ped Surg* 2023; 58:2399-2404.

PSORC Corner

The Pediatric Surgical Oncology Research Collaborative (PSORC) continues to grow. PSORC is a collaborative effort between 41 institutions committed to improving surgical outcomes for pediatric patients with cancer through multi-institutional investigation. To date, PSORC has published 16 abstracts and 12 manuscripts, with more on the way from recently completed projects.

Current projects include a comprehensive study evaluating surgical outcomes of pediatric patients with neuroblastoma and a study assessing contemporary surgical approach to adrenocortical carcinoma. Additionally, the Fibrolamellar Cancer Foundation is supporting a study that expands on a previously established PSORC database of pediatric rare liver tumors and seeks to identify how fibrolamellar carcinoma differs from hepatocellular carcinoma. Upcoming projects focus on defining guidelines for the surgical management of ganglioneuroma, improving the diagnostic accuracy of indeterminate thyroid nodules, and assessing how to manage immature teratoma considered not fully resectable.

Anyone interested in joining PSORC is encouraged to email the Chair, Roshni Dasgupta, MD, MPH (Roshni.Dasgupta@cchmc.org).

website: www.psorc.org
twitter: @PedSORC

Pediatric Surgical Oncology Research Collaborative

Operative Standards for Pediatric Surgical Oncology

The October 2023 Edition of *Seminars in Pediatric Surgery* is focused on pediatric surgical oncology. While this topic has been a focal point in the past, the format of these articles is unique. The background is important to explain this difference. Two of the editors of the work, Drs. Doski and Gow, have had roles with the Commission on Cancer. This organization is a joint endeavor between the American College of Surgeons and the American Cancer Society. Its goal is to elevate the overall delivery of cancer care for patients in the US. The CoC is made up of 59 organizations that each have representation in the administration of the Commission. Both APSA and the AAP have member representation on CoC, which Drs. Doski and Gow are currently serving. In this role, they learned of a continuing project entitled Operative Standards for Surgical Oncology which were in the form of handbooks. Each covered a series of cancers by acknowledged experts that described the standard approach for relevant cancer operations and provided evidence on why this is important. The ACS supported the pediatric surgeons to produce a similar handbook and experts were selected and the work was begun prior to 2020. While this did not come to fruition in its originally intended format, after discussion with Drs. Davidoff, Dasgupta, and Ostlie, we found a new home to publish these works in *Seminars in Pediatric Surgery*.

The format is different from the standard chapter or reviews. The focus is on the critical elements of the surgical procedure. Thus, it is more similar to a surgical atlas than it is a review. The assumptions are; i) that the operation is warranted and advisable for the patient, and ii) you have the experience to perform the operation(s). The text provides the important steps and goes into them in detail at a fellow or higher level of comprehension. The evidence for these steps has also been evaluated by the authors. Of note, while the evidence may in some respects be per expert opinion and not based on randomized control trials, the authors are acknowledged leading experts in these procedures.

The second aspect that was included was the clinical staging. While these are available in other sources, assembling them together here in one location provided us a unique opportunity to be able to reference this for future work. While this may not seem like an important matter, we only need to understand the difference between pediatric and adult cancer staging. While we have grown accustomed to having a unique set of staging for each pediatric solid tumor, adult tumors have adopted the American Joint Committee on Cancer (AJCC) cancer staging which is used and published with updates and serves as the acknowledged standard reference. Since the beginning of pediatric oncology, such a standard text has not been available. As such, there has been no published source that one can make available for the use of databases such as the Surveillance, Epidemiology, and End Results (SEER) Program, and the National Cancer Database (NCDB). As a result, those databases have not been able to provide patient specific staging for pediatric solid tumors. This limits its effectiveness for research.

The editors of this volume of *Seminars in Pediatric Surgery* would like to thank the authors for their tireless work on assembling a one of a kind publication. Further, we hope this becomes useful for all pediatric surgeons who provide care for their patients.

Contributed by Kenneth Gow, MD

Full reference:

Dasgupta R, Doski J, Gow KW. Operative standards for pediatric cancer surgery. *Semin Pediatr Surg*. 2023 Oct;32(5).

Living Legends in Pediatric Surgical Oncology: Michael LaQuaglia

Michael P. LaQuaglia was invited to participate in a fireside chat at a recent COG meeting. This article reflects the proceedings of his interview.

Dr. LaQuaglia, who has done full-time pediatric surgical oncology for his entire career, was born in New Jersey and trained at the Massachusetts General Hospital and the Boston Childrens Hospital. This also included a stint in Liverpool, England where he learned the thoracoabdominal incision. Dr. LaQuaglia indicated his great appreciation for the quality of his training, and the guidance of superb mentors.

As a pediatric surgical fellow in the late 1980's he observed the great advances in Wilms tumor therapy that had been made in previous decades. In contrast, the overall survival with high- risk studies confirmed high-risk neuroblastoma and this news had a devastating effect on the family.

This episode plus the fact that his pediatric surgical mentors, including Drs. Patricia Donahoe, and W. Hardy Hendren, had encouraged trainees to look for hard problems to solve, stimulated Dr. LaQuaglia to follow a career in pediatric surgical oncology. At the same time, a position had opened at Memorial Sloan Kettering Cancer Center(MSKCC). Also, Dr. Nai-Kong Cheung, who had pioneered the use of antibody therapy for neuroblastoma was recently appointed head of the neuroblastoma team there and Dr. Brian Kushner, who had done many early trials of chemotherapy for neuroblastoma, was a colleague as well. In preparation for the move to MSKCC Dr. LaQuaglia read all the published articles on neuroblastoma surgery by Drs Gross, Koop, Grosfeld, Tsuchida, Kaneko, Atkinson, Haase, DeBernardi, Shochat, and others.

Dr. LaQuaglia believed that neuroblastoma resections were guided by the principle R1 resection. (R0 resection is almost never possible with neuroblastoma because of infiltration of vital structures). He emphasized, "that Drs. Kushner and Cheung were greatly supportive of this approach and would often come to the operating room as observers". This was a great stimulus to undertake very complicated and grueling resections.

Dr. LaQuaglia's impact extends beyond neuroblastoma and includes papers on pediatric thyroid cancer, melanoma, the pediatric sarcomas, fibrolamellar hepatocellular carcinoma, and desmoplastic small round cell tumor. Throughout his career, he championed collaboration within the Childrens Oncology Group (formerly CCSG and POG) and within institutions where at least two surgeons could work collaboratively on tumor cases. Further, as tumor management becomes more complicated, Dr. LaQuaglia indicated that "institutions should concentrate management to select surgeons with interest and expertise".

Dr. Michael LaQuaglia's journey epitomizes a relentless pursuit of solutions to unsolved problems in pediatric surgical oncology, making him a beacon of inspiration for future generations in the field.

The editors would like to thank all those that contributed to this first edition of *Surgical Aims.*
If you would like to contribute COG updates in a future issue, please contact one of the editors:
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