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NEWSLETTER

APPENDIX CANCER & PSEUDOMYXOMA PERITONEI (PMP)

PATIENT. CAREGIVER. COMMUNITY.

PMP Pals is pleased to bring you this special edition of our newsletter, devoted to an interview with **Paul H. Sugarbaker, MD**. As part of our **Focus on Physicians** series, this article highlights his four decades of leadership in the treatment of peritoneal surface malignancies, including appendiceal cancer and pseudomyxoma peritonei (PMP).

Our board member **Charmaine** interviewed Dr. Sugarbaker, who performed her life-saving surgery in 2009.

We hope you enjoy this newsletter. Let us hear from you at info@PMPPals.net

Board of Directors

Chris, Adele, Charmaine, Libby, and Mark

FOCUS ON PHYSICIANS
PAUL H. SUGARBAKER, MD

By Charmaine Skillman, PMP PALS, Board, Secretary

Let's start with the question many are asking: are you "retiring"?

Not exactly. I will no longer be performing 10-12-hour surgical procedures at Washington Hospital Center. Through 2020, I had continued to perform up to two cytoreduction surgeries (CRS) per week. But it is time for me to prioritize my time and energy to new projects. Starting in 2021, instead of treating individual patients, I will focus my efforts on a critical analysis of the data on peritoneal surface malignancy patients I've handled over my career. This will allow me to evaluate our treatment strategies and present them in a way that will show patterns and lessons.

FOCUS ON PHYSICIANS
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By Charmaine Skillman, PMP PALS, Board, Secretary

I will focus my efforts on a critical analysis of the data on peritoneal surface malignancy patients I've handled over my career.

What about the annual update that patients send you, or former patients with a need for consultation due to developments after surgery?

I will continue to track patient outcomes through the updates, and I will still be available for consultation.

Let's talk about some of your projects.

I have been working on 35 case reports, surgical short stories, that take a deep look at interesting patients I have cared for. I will publish these individually and as a book. These reports provide insight into unusual PMP management issues that can be instructive for the future.

Please tell us about a much larger project involving all of your patient outcomes.

Together with David Chang, a statistician, I am going through 2,000 patient files to analyze the data on outcomes. Of the 2,000 files representing more than 20 years of surgery at Washington Hospital Center, we've gathered cause of death data on all but a few patients. We will present a complete report on patient outcomes and survival rates. This will be the sixth time since 1995 that I have reported on all of my results for patients with appendiceal cancer with peritoneal metastases -- treatments and outcomes. It will be my fourth time reporting on results for colon cancer with peritoneal metastases. Though not randomized studies, this kind of large retrospective study of outcomes can lead to important clues about what treatments work best. My records include over 1,200 appendiceal cancer patients.

In these records, we also have 247 colon cancer patients with peritoneal metastases. Of these, about 35 patients survived at least ten years. We seek to identify what was unique about them. We are looking at more than 20 factors to determine the effect on survival. Longer-term survival appears to be associated with having complete cytoreduction surgery. And, we see some indication that neo-adjuvant chemotherapy prior to CRS may be helpful – a finding that I find surprising but deserves more investigation. We have sent our early results to the American Society of Colon and Rectal Surgeons.

These data are important to the colorectal surgeon because we sometimes still encounter resistance to CRS – it's viewed as an overly-aggressive surgery for patients who supposedly will die anyway. The hopeful news is that long term, disease-free survival is possible for colon cancer patients with peritoneal metastases.

This project certainly will be instructive given the large number of cases handled by one lead surgeon at one hospital center. You also are working on another scholarly article with a different focus, right?

Yes, I am working on a special issue of the Journal of Gastrointestinal Oncology in which we will publish about 20 manuscripts focused on cutting edge data regarding HIPEC from around the world. Some of these treatment ideas are controversial, but this can stimulate interest and research efforts in peritoneal surface malignancies, including gastric and ovarian cancers.

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What about your work with PSOGI?

I will remain active as the General Secretary of Peritoneal Surface Oncology Group International (PSOGI). We are preparing for the upcoming PSOGI Congress to be held September 2021 in Beijing. We expect a strong interest in the program, with large in-person attendance from China and virtual attendance from other parts of the world due to the on-going impact of Covid-19.

Another PSOGI project is an article, to be published around mid-2021, that will look at how to determine the best form of intra-peritoneal chemotherapy to use after a complete CRS. Marcello Deraco, MD, a leading expert in consensus by the Delphi method, will process the recommendations by physicians world-wide. We will look at comparative benefits of different forms of intra-peritoneal chemotherapy (HIPEC, EPIC, NIPEC, and more) when there is complete CRS. We hope to lay the groundwork for randomized clinical studies on these treatment alternatives.

We also hope to see more single institution studies in high volume centers comparing outcomes from different chemo agents after CRS. One study will use peri-operative FOLFOX compared to the "old standard" Mitomycin-C. We may see that patients do better with a more aggressive chemo agent than the Mitomycin-C we have been using the most.

That brings to mind a question about adjuvant chemo either before or after CRS. It seems more and more patients say their surgeons now recommend adjuvant systemic chemo. Do you see this as well?

Yes, I do see systemic chemotherapy being used more frequently both before and after CRS/HIPEC. But I have concerns about systemic chemotherapy use. In some cases, some components of the dissection of peritoneal metastases during CRS may be thought of as "too dangerous." The surgeon may decide to leave it to systemic chemo to deal with the tumor that remains. In my view, this results in an incomplete CRS. There is no such thing as a cure if you don't remove all visible tumor. HIPEC plus systemic chemotherapy enhances the survival rate, but you still need a complete cytoreduction for optimal results. If this approach is contributing to an increase in incomplete CRS, it is not a good development for patients.

With regard to the colon cancer patients you mentioned earlier, those who can benefit from CRS and from HIPEC, we still hear some resistance to HIPEC. Can you comment on a French study from about 3 years ago and how it is affecting use of HIPEC for colon cancer patients with peritoneal metastases?

This French study, known as Prodigy 7, found that there was no statistically significant effect from HIPEC on these colon and rectal cancer cases. But the study looked at cases in which the patients were treated with systemic chemo before surgery; then, the HIPEC chemo agent was the same as the systemic chemo agent that had been used. You cannot expect to see improved outcomes from HIPEC if you have already killed off the cells receptive to that HIPEC agent. You cannot use the same drug this way and expect to see HIPEC improve outcomes. So, despite this flaw in design, the Prodigy 7 study has depressed the use of HIPEC for colon cancer patients who could benefit from the procedure. In my opinion, the efficacy of HIPEC for such cases remains an open question, but this study makes it harder to convince medical oncologists that HIPEC is of benefit for colon cancer patients.

Let's talk next about the challenge of finding the right treatment by the right surgeon. It is difficult for a patient to find out about a surgeon's experience and a HIPEC center's outcomes. What can be done to make it easier to find the right treatment?

I am very critical about the lack of any centralized approach to establishing CRS/HIPEC centers in the U.S. or for tracking results of treatment. And, there is no compulsory gathering of morbidity and mortality data at these CRS and HIPEC centers. There are more than 200 places in the U.S. performing HIPEC but only a few report their data.

The medical corporations prefer to have no data reported at all than for possibly negative data to be reported. You're right – it makes it hard for the patient to assess the surgeon and the hospital.

In Europe, PSOGI has a joint project with the European Society of Surgical Oncology (ESSO) to promote a more standardized training for performing CRS/HIPEC. It is known as the European School of Peritoneal Surface Malignancies ("ESPSM"). It is a two-year curriculum that can be accomplished at a medical institution with the resources and interest to support the endeavor. There must be a mentor, a required number of mentored procedures, attendance at educational courses, and preparation of a scholarly manuscript. This school is not a perfect solution, but it offers much more consistency in training than what we see in the U.S. There is no comparable program in the U.S. All that is required here is to finish a surgical oncology fellowship; then, any surgeon can begin performing highly complex CRS and HIPEC with little or no specialized training.

Patients should understand that what happens before you get to the cancer center of excellence can have consequences for the outcome of subsequent surgery. For example, for women with ovarian cancer who have had surgery for ovarian tumors and later seek more extensive cytoreduction surgery, extensive prior surgery can reduce long-term survival by as much as 50 percent.

This is because in the initial surgeries, which include pelvic lymph nodes dissections, the tumor cells can be driven deeper into inaccessible areas – an effect known as tumor cell entrapment (TCE). The TCE from the first surgery can dramatically affect the success of later surgery.

Speaking of lymph node involvement, appendix cancer patients frequently say that their surgeons are performing right hemicolectomies to remove lymph nodes on a preventative basis. This seems to be happening frequently – your thoughts?

The reason given for removing the right colon usually is to prevent "occult" (unseen, undetected) lymph node metastases. But, in a study I co-authored with a former fellow, Santiago Gonzalez-Moreno, MD, we looked at clinical data for 500 right colon resections in patients with appendiceal mucinous neoplasms in order to re-evaluate the surgical judgment for the hemicolectomy.

We found that the incidence of occult lymph node metastases (that is, any cancerous cells that cannot be seen) was less than 5 percent. So, the data show no survival advantage from a right hemicolectomy for patients with mucinous carcinoma of the appendix and peritoneal seeding (i.e., well-differentiated mucinous carcinoma). It is only when you are dealing with adenocarcinoid tumors – the goblet or signet ring cells-- that removal of the right colon is important because there is a 30 percent incidence of lymph node metastases.

We concluded that right hemicolectomy should be avoided unless there is metastatic involvement of the appendiceal or distal ileocolic lymph nodes documented by biopsy, or the resection margin is inadequate.[1] Patients need to discuss this thoroughly with their surgeon and seek a second opinion from an experienced specialist.

What guidance do you have for patients in choosing a surgeon?

PMP Pals should educate patients on how important experience and training are for the outcomes. Kiran K. Turaga, MD, MPH recently published a study that assessed the surgical workforce for CRS/HIPEC.[2] The study concluded that little is known about the doctors performing these complex surgeries. Unlike for comparably complex oncological procedures, there are no training requirements or requisite experience for CRS/HIPEC in either residency or fellowship. Further, without a thorough understanding of the disease processes, the true complexity of CRS/HIPEC may be underestimated, and some surgeons performing the procedures may lack the experience and support to achieve adequate oncologic outcomes while maintaining patient safety. With the number of HIPEC centers growing, the study found that almost twenty percent of surgeons performing these procedures essentially have less than three years of experience since completing their surgical training.

We can say that the greater the experience of the surgeon, the greater the surgeon's ability to perform a complete CRS and thus the greater the survival benefit. The article advocates that fellowships in surgical oncology should develop additional training standards, such as requiring experience with cytoreduction and intraperitoneal chemotherapy. It also advocates that formal mentorship requirements should be established for less experienced surgeons performing these procedures.

The article highlights an important concern: where to seek treatment and from whom. Just finding the specialists and the HIPEC centers can be a challenge. Then, the patient must balance personal factors, such as travel and insurance coverage. Your thoughts?

In the U.S., it can be quite disorganized and hard for a patient to decide how to proceed. I have advocated a more centralized system of providing CRS/HIPEC for peritoneal surface malignancies, but my position is not popular among U.S. surgeons. In Europe, there is more movement towards a centralized approach to establish standards of expertise and help patients find expert treatment.

One example is in the United Kingdom, where Basingstoke is the center for these procedures. It is a much more organized system to help patients access expert care. There is more support for patients, such as a reasonably-priced hotel for patients and families to use.

Another example is Sweden, where there are five centers to provide CRS/HIPEC; no other hospitals are permitted to perform the procedures.

In the U.S., the economics of caring for rare diseases such as peritoneal mesothelioma with PMP or appendiceal cancer with PMP make it harder to get care. Hospitals are more reluctant to commit the resources needed to treat the relatively small number of patients with rare diseases – equipment, staff, space. And, restrictive preferred provider insurance arrangements, including many Medicare Advantage plans, make it more difficult for patients to have coverage for treatment by specialist providers. A plan may cover a surgeon close to home because the plan is designed for treatment in a certain geographic area, but if you need to see a surgeon at a national cancer center of excellence, the plan may not cover that medical care.

In the U.S., we don't take care of patients with rare diseases as well as we should. There is a lot that needs to change—from training to qualifications of surgical centers to insurance coverage to reporting of outcomes.

"We started with no cures 35 years ago. The fact that we even treat patients with peritoneal metastases today is a huge difference ... I knew these patients could be treated; I knew that many could be cured. Now, management of peritoneal metastases is a reality."

[1] See, S. Gonzalez-Moreno, P.H. Sugarbaker, et al. "Right Hemicolectomy Does Not Confer a Survival Advantage in Patients with Mucinous Carcinoma of the Appendix and Peritoneal Seeding" The British Journal of Surgery, Vol. 9, Issue 3, pp. 304-311 (Mar. 2004).
[2] See, Schuitevoerder, D., Sherman, S.K., Izquierdo, F.J. et al. "Assessment of the Surgical Workforce Pertaining to Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in the United States" Annals of Surgical Oncology Vol. 27, pp. 3097–3102 (2020).

We agree, there is still a lot to be done to help patients get the care they need. Shifting focus, I'd like hear about how CRS/HIPEC came to be accepted over the years. And, how did this surgery come to be known as the "Sugarbaker procedure"?

When I began as a surgeon, we were taught to preserve the peritoneum at all costs. It was standard dogma – it was taught that if you resected the peritoneum, the abdomen and pelvis would become a fibrotic mass and the bowels would no longer function. I found that you could indeed remove all of the parietal peritoneum and a good amount of the visceral peritoneum and the intestines would work just fine. I invented and popularized the right upper quadrant, left upper quadrant, anterior abdominal wall, and pelvic peritonectomy. I found that by removing the peritoneum so as to remove the peritoneal metastases, the patient could survive and the bowel would function. Second, I insisted that the cancer resection should take place with a single surgery. The surgeon must operate for as long as it takes, twelve or more hours, to remove all visible tumor, to achieve a "zero" Completeness of Cytoreduction Score (CC-0), meaning, no visible tumor left and little likelihood of remaining cancerous tissue. These are the patients who survive long-term. Third, I travelled all over the world, teaching these procedures, as well as publishing extensively about peritoneal metastases treatments.

At one point, I was at Basingstoke, working with Mr. Brendan Moran and Mr. Bill Heald to establish a PMP referral center under a project sponsored by the National Health Service. An investigator with the Service wrote up what I was doing; he described the necessary parts such as the peritonectomy and the heated wash during surgery. He was the one who called it the "Sugarbaker procedure" and the name stuck, even outside the United Kingdom.[3]

Patients today may not grasp how different the goals of treatment are now compared to when you first started treating peritoneal surface malignancies from appendiceal cancer, mesothelioma, and ovarian and colon cancer.

In the early 1980s, peritoneal metastases from these cancers were considered a completely terminal clinical situation. So, the attitude was that nothing could be done to save the patient. In fact, the condition used to be referred to as "carcinomatosis" -- which implied a fatal event for which palliation was the approach. We changed the terminology to "peritoneal metastases" – which was similar to other conditions for which there was treatment. The new terminology implies there is serious disease but something can be done.

We started with a program to have intra-peritoneal chemo after surgery – known as EPIC, then added HIPEC, and the management of peritoneal metastases grew from there. We started with appendiceal cancer with PMP and had success with treatment.

[3] Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P. Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei. Health Technol Assess. 2004 Feb;8(7):iii, 1-54. doi: 10.3310/hta8070.

The reason I have more than 1,200 appendiceal cancer patient files is that Washington Hospital Center was a big referral center for this disease and we had good institutional support then. We published important articles showing peritoneal metastases can be cured. Treatment expanded to peritoneal metastases caused by mesothelioma, colon cancer, and ovarian cancer. Now, ovarian cancer patients with peritoneal metastases are probably the largest group of patients getting CRS/HIPEC around the world. I would sum it up this way. We started with ***no cures*** 35 years ago. The fact that we even treat patients with peritoneal metastases today is a huge difference. Now, we are routinely treating these cancers that have metastasized into the peritoneum and having much greater success than in the early days. Early in my career, I was criticized as being overly aggressive for treating patients who "were going to die anyway." But I knew these patients could be treated; I knew that many could be cured. Now, management of peritoneal metastases is a ***reality***.

If you were advising a young surgeon on treatment innovation, what would you say?

First, you must have a good idea, something that works. You then accumulate the data to support your innovation, establish adequate controls, and make an elegant presentation. Mostly, you must have persistence. You must be resilient, don't let people knock you down, and if they do, get back up.

Before we close out this interview, I want to mention your wife Ilse, who has been your office manager all these years. For many patients, she was the first person we talked to when setting up our CRS/HIPEC. She advised us on insurance and talked us through so many aspects of preparation. We want to express our appreciation for all she has done for so many patients.

Thank you for mentioning her contributions. After so many years of this work, she is looking forward to having time for other interests.

Finally, you have been a supporter of PMP Pals for years -- you've welcomed our participation at PSOGI symposia and enabled us to connect with surgeons around the world. What are your thoughts about PMP Pals' role?

There is a need for PMP Pals in every major country. For example, India and Brazil are huge countries with active HIPEC programs. They have large patient populations that PMP Pals can help. Your group provides support and information, and that's needed everywhere.

"Your group provides support and information, and that's needed everywhere.

THANK YOU

DR. SUGARBAKER

Our sincere thanks to Dr. Sugarbaker for this interview and, more importantly, for his dedication in treating thousands of patients, as well as his mentorships and scholarly works that enabled thousands more around the world to receive treatment.

We look forward to his on-going work that will continue into the future.

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PMP Pals is the world's oldest global volunteer-run organization that gives hope to patients and caregivers fighting Appendix Cancer and Pseudomyxoma Peritonei or PMP.

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