INTERVIEW

Colorectal Cancer
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The evolution of treatment for peritoneal metastases

Paul H Sugarbaker* speaks to Theo Bond, Assistant Commissioning Editor: Dr Sugarbaker was born in Baltimore (MD, USA). His college education took place at Wheaton College in Illinois. He graduated from Cornell University Medical College in New York (USA) and from there went for his surgical training at the Peter Bent Brigham Hospital in Boston (MA, USA), now known as Brigham and Women's Hospital. He received a Masters Degree in Immunology at the Harvard School of Arts and Sciences in 1983. At the NIH he was a Senior Investigator from 1976 to 1986. After a brief stay in Atlanta at the Emory Clinic he moved back to Washington (DC, USA) to become the Medical Director of the Washington Cancer Institute. He has been at the Washington Cancer Institute since 1989. Currently, he is Medical Director at the Center for Gastrointestinal Malignancies and Director for the Program in Peritoneal Surface Oncology. His interests are in gastrointestinal cancer, gynecologic malignancy and mesothelioma. For many years his work focused on liver metastases. Currently, his clinical and investigative work is directed at the peritoneal surface component of gastrointestinal cancer dissemination, referred to as peritoneal metastases. Dr Sugarbaker is a strong critic of surgical tradition; he believes that major changes in the technology of cancer resection are necessary. His theme, 'It's what the surgeon doesn't see that kills the patient', summarizes the concepts behind many of his publications both in the peer-reviewed medical literature and in the lay press. In the opinion of Dr Sugarbaker, perioperative intravenous and intraperitoneal chemotherapy are an essential planned part of many cancer interventions.

Q After completing your residency at the Peter Bent Brigham Hospital, how did you become interested in colorectal cancer?

Colorectal cancer was part of my surgical training; I was fortunate to have Joseph Murray, the Nobel laureate, as one of my surgical mentors. Joe was a kidney transplanter at the time but also a plastic surgeon. While working on cases and at social events, I received advice from Joe Murray that if I wanted to be successful at surgical problem solving then I should become an expert in a well-defined field that I could talk about and develop an established background to ask in-depth questions about the field. I went looking for a project to explore. As it turns out, when I was at the Peter Bent Brigham Hospital, the carcinoembryonic antigen (CEA) had just been discovered by Michael Gold. In addition, Norman Zamcheck, who ran the Mallory Gastrointestinal Laboratory at the Boston City Hospital (MA, USA) was actively involved in clinical research with CEA. I, somehow or another, became the CEA blood test coordinator for the Brigham Hospital. I basically kept blood tubes in

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my pocket and went around drawing blood in order to determine the clinical value of CEA blood tests. For example, what was the role of CEA in determining prognosis? What was its role in the diagnosis of recurrence in follow-up? What happened when you monitored radiation therapy for rectal cancer with serial CEA? Therefore, we put together a series of manuscripts trying to demonstrate the role that CEA should play in colorectal cancer management. This was a successful project.

CEA is now a standard test used for managing colorectal cancer. It is remarkable how a CEA prior to a rectal cancer resection of 30 ng/ml will go down to 1 or 2 ng/ml after a complete resection. In follow up of patients over 2 or 3 years you may see it gradually begin to rise again. We tried to define what was a significant rise with serial CEA determinations. We compared it to CT scans, which were just coming out, and tomograms. We did establish the role of CEA and second-look surgery; finding that with serial CEA assessment we could predict a recurrence of colon or rectal cancer about 6 months prior to radiologic tests. Overall we developed a very successful project on CEA and its role in second-look colorectal cancer surgery.

When you are a surgical resident it is difficult to decide "I'm going to become a colorectal surgeon or a breast cancer specialist"; it is more about being opportunistic. It turned out that Hiromi Shinya, who was then at the Mount Sinai Hospital (NY, USA), accepted me for a very brief fellowship in fiberoptic endoscopy. I was the only one who had a colonoscope in the whole of the New England region for several years. We began doing colonoscopy polypectomy and diagnostic colonoscopies, in addition to making movies about how to do colonoscopy. This led to a number of successful publications in peer-reviewed journals. The CEA and the colonoscope were the foundations of my career in colorectal cancer.

Q You were appointed Head of the Colorectal Cancer Section at the National Cancer Institute (NCI) in Bethesda (MD, USA) in 1981, how has colorectal cancer therapy developed since then?

When I started at the NCI Surgery Branch, there was a single manuscript in the literature by Wilson and Adson, which was published as part of a Western Surgical Association meeting [1]. Martin Anderson had collected approximately 20 years of experience with resections of colorectal liver metastasis and liver surgery was not done at that point in time for two reasons:

- Surgeons thought that if you cut into the liver deeply, the patient would bleed profusely;
- Both surgeons and oncologists were convinced that liver metastases were not local–regional in any way but were always a sign that there was systemic disease. Therefore, it was an exercise in futility to remove one, two, three or more liver metastases.

We started a program at the NCI Surgery Branch to resect liver metastases. It is hard to believe now that there would be so much prejudice against the surgical removal of liver metastases. I can tell you that at this point in time that it was a real uphill battle. I can remember presenting cases, where the oncologists would laugh that we had removed three liver metastases from a patient. Kevin Hughes and I went all over the country collecting data on approximately 900 liver resections. This was a multi-institutional study of patients who had survived liver resection for colorectal malignancy. We defined the parameters for colorectal resection. This was really the first large multi-institutional study of the important prognostic factors in liver metastases and changed the opinion of oncologists about how to treat the disease.

Q What do you consider the biggest achievement in your career?

The transition from a focus on liver metastases to peritoneal metastases was very important. Surgery for peritoneal metastases is more demanding than surgery for liver metastases. The development of the peritonectomy procedures and the parameters whereby patients would be selected for a curative approach for peritoneal metastases was an evolutionary process. One successful strategy for colorectal metastatic disease

led to additional treatments, which are now cytoreductive surgery, hyperthermic perioperative chemotherapy (HIPEC), placement of an intraperitoneal port, long-term combined intraperitoneal and systemic chemotherapy. This strategy is still developing; we are trying to find the optimal treatment for a bidirectional approach cancer therapy.

Q You are currently Director of the Program in Peritoneal Surface Oncology at the Washington Cancer Institute, what colorectal research are you currently carrying out?

A major current clinical project is to establish algorithms. The research that we are carrying out in colorectal malignancy is basically data gathering. The institutional review board has approved protocols in pancreas malignancies on which we are currently working. We are trying to improve local–regional control as part of the surgical procedures for foregut malignancies. The current project is with combined heated intraperitoneal gemcitabine and systemic Abraxane (nanoparticles of paclitaxel). Furthermore, we are trying to define the role of this perioperative chemotherapy in pancreatic cancer. What we hope to define is neither neoadjuvant chemotherapy nor adjuvant chemotherapy. It is perioperative chemotherapy; chemotherapy actually used by the surgeon in the operating room to eliminate local–regional recurrence and peritoneal dissemination. It is a very well-defined project with limited goals, which are to eliminate the local recurrence and peritoneal metastases from colorectal, pancreatic and other gastrointestinal malignancies. We are using the information that has been established for colorectal cancer to expand to ovarian and other gastrointestinal malignancies.

Q What role does personalized therapy currently have in colorectal cancer treatment?

Personalized therapy may be the most important task that the multidisciplinary team needs to perform. If you have a patient with peritoneal metastases from colorectal cancer and you treat that with systemic chemotherapy, and that is the extent of the treatment, then in my personal opinion, you have done that patient a major disservice. Up to 50% of patients with peritoneal metastases from colorectal malignancies can be cured. We are talking about a median survival of 4 years and a long-term survival of 40%. This is in contrast to a median survival of 16–18 months and 2–3% 5-year survival with systemic chemotherapy alone. Therefore, you need to personalize the approach.

We are now performing what we call proactive treatment for peritoneal metastases. Approximately 20% of patients with colorectal malignancy will present with peritoneal metastases and approximately half of those are candidates for HIPEC treatment as part of the primary colorectal cancer resection.

Q How will colorectal cancer therapy progress over the next decade?

Our major effort right now is education. How many surgical oncologists are proficient in the management of peritoneal metastases? Very few. How many centers for treatment of peritoneal metastases are there in the USA now? Very few. Of these centers how many can deliver a high quality of treatment with optimal likelihood of long-term survival and a minimal likelihood of an adverse event? We need more formal courses to promote optimal management of peritoneal metastases. Currently, we have many regional meetings for education in peritoneal surface oncology around the globe. Also, the Biannual International Meeting will be in Amsterdam, 8–11 October 2014. We expect 800–1000 participants for this 'global attack' on peritoneal metastases.

A second clinical research effort is to optimize our perioperative and long-term management strategies for pancreatic cancer. We are in the process of accruing 36 patients with primary pancreas malignancy to be treated with hyperthermic intraperitoneal gemcitabine plus Abraxane followed by 6 months of combined intraperitoneal gemcitabine and intravenous Abraxane. Our early results are very promising.

Q Do you believe that colorectal cancer will ever be cured?

No, I am not optimistic that we will find a cure. But, I am very interested in prevention of this disease and the prevention of

the progression of the disease after surgical treatment. I think that perioperative chemotherapy can go a long way towards reducing the number of patients who have a recurrence. One of my highest priorities in the search of better outcomes is to have colon cancer patients who are at high risk for peritoneal metastases, either before or after their primary resection, identified and treated proactively with cytoreductive surgery combined with HIPEC.

The old saying "an ounce of prevention is worth a pound of cure" applies to virtually every patient with primary gastrointestinal malignancy. A good example of our success occurs with appendiceal malignancy. 20 years ago the patients we evaluated had a large volume of mucinous malignancy, referred to as pseudomyxoma peritonei. Now, most of our patients come to us with a perforated malignant mucocele, a small volume of mucinous ascites and a very high likelihood of cure with a greatly simplified intervention.

My take-home message would be to move cytoreductive surgery and HIPEC up into the primary treatment of appendiceal cancer, colorectal cancer, small bowel adenocarcinoma, gastric cancer and pancreatic cancer. Why shouldn't chemotherapy be a standard part of surgical management in properly selected patients? This is happening much more quickly than I had expected around the globe in the management of gastrointestinal malignancy.

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Reference

1 Wilson SM, Adson MA. Surgical treatment of hepatic metastases from colorectal cancers. *Arch. Surg.* 111(4), 330–334 (1976).