

Editorial

Appendiceal Malignancy: Where Do We Stand?

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The manuscript by Sugarbaker and Chang¹ in this issue of *Annals of Surgical Oncology* is quite significant in that it represents, by far, the single largest series of patients with appendiceal tumors and peritoneal spread of disease. It represents the summation of the many years of experience for the surgeon most closely associated with this disease. The incidence of this extremely rare disease is not truly known. In some ways it represents a spectrum of diseases, thus presenting a greater challenge for surgeons, especially as most surgeons only rarely encounter it. In determining prognosis, Sugarbaker and Chang emphasize the influence of the extent of prior surgery, degree of completeness of tumor debulking, and histology. Other important prognostic factors will be discussed below. During Dr. Sugarbaker's long experience with this disease, his strategies for managing this disease have evolved over four distinct approaches and they are mentioned in his report. It would be illuminating to learn what insights led him to these changes.

Unlike most diseases of the gastrointestinal tract that develop carcinomatosis or peritoneal spread, cancer of the appendix tends to present an ongoing problem for the surgeon. Patients with pancreatic or gastric cancers whose tumors have spread to the peritoneal cavity have a median survival of approximately 5 months. Most die of disease within 1 year. The rapid demise of these patients frequently takes them out of the surgical arena and demands approaches for systemic therapies or palliative and supportive measures. In contrast, carcinoma of the appendix has a median survival measured in years, and patients frequently require multiple operations. Although the disease is usually of low biologic aggressiveness, a small subset of patients die of disease within a few months of first diagnosis.

A significant article on tumors of the appendix was reported in *Cancer* in 1994.² This report by Carr et al. examined 184 patients with noncarcinoid tumors of the appendix, reviewed at the Armed Forces Institute of Pathology (Rockville, MD). These authors attempted to classify the lesions according to pathology as well as specific clinical factors. The classifications included simple mucocele, hyperplastic polyp, adenoma, mucinous tumor of UMP (uncertain malignant potential), and adenocarcinoma. Within this cohort, 82 patients had complete follow-up. Of these, 15 had tumors of UMP and 64 had carcinomas. The 5-year survival rate was 65%. The authors were able to identify two significant factors that were prognostic in patients with mucinous tumor of UMP or adenocarcinoma. The first was the presence of mucin cellularity. The presence of cellular mucin deposits located outside the appendix conveyed a statistically significant decrease in survival, to < 40% at 5 years vs. 80% without cellular mucin. Similarly, the presence of mucin outside the right lower quadrant resulted in a 5-year survival rate of < 40% compared with nearly 80% in the absence of this finding. The pronounced differences in survival underscores some of the difficulties in evaluating various treatment regimens.

A second important study of appendiceal cancer was from the Mayo Clinic and reported in *Annals of Surgery* by Nitecki et al.³ In this study, patients with advanced disease had a median survival of about 24 months with a 6% 5-year survival. Nodal resection achieved by right hemicolectomy significantly improved survival. Perhaps the most important finding was that in 38% of patients who had hemicolectomy as a secondary procedure, nodal disease was found. This could change one's decision about peritoneal-based therapy.

Another report on patients with these tumors also comes from the Mayo Clinic by Gough et al.⁴ They reviewed 56 patients who were treated for pseudomyxoma between 1957 and 1983, and roughly half had tumors of the appendix. Despite removing all gross disease in only a third of the patients, and finding

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that tumor progressed in 76% of the patients, the 5- and 10-year survival rates were 53% and 32%, respectively. In this study, preoperatively prognostic factors, including weight loss and abdominal distention as well as the use of systemic chemotherapy (patients with greater tumor burdens may have been selected for systemic chemotherapy), were predictors of poor survival. Most important was that the use of intraperitoneal chemotherapy and/or radiotherapy improved survival significantly, though the number of patients was quite small.

This brings us back to the remarkably large series reported by Sugarbaker and Chang¹ in this issue of the *Annals of Surgical Oncology*. No comparison is made among the four different treatment regimens used; however, because the most recent group of patients has had only limited follow-up, such analysis may not yet be possible. In a report 3 years ago by Sugarbaker et al.,⁵ many pathological and clinical factors were found to be not significant. It would be interesting to see if this much larger cohort of patients provides the statistical power needed to demonstrate prognostic significance for some of these factors, such as lymph node involvement.

Dr. Sugarbaker's experience with intraperitoneal perfusion mirrors our own experience at The University of Texas M.D. Anderson Cancer Center, where, since 1992, we have used intraperitoneal mitomycin C combined with hyperthermia after extensive tumor debulking. We have taken this approach in selected patients who have either metastatic mucinous adenocarcinoma or poor prognosis tumors of UMP as defined by Carr et al.¹ In the 24 patients that we have treated, there has been a > 75% 5-year actuarial survival rate.

Perhaps the most intriguing statistic in this report by Sugarbaker and Chang¹ is the dramatic increase in the

number of patients seen recently. In slightly over 1 year (December 1997 to January 1999), more than 200 patients were managed by this group. This is most likely a reflection of the extensive use of the Internet by patients and physicians to identify potential treatment options; we also have seen a rapid increase in referrals and inquiries originating via the Internet. Although an aggressive approach at the first or second operation may provide the greatest likelihood for prolonged survival, because sufficient numbers of patients with this disease appear to exist, it behooves us to conduct the appropriate multi-institutional randomized trials. The authors, with their preeminence in the study of this disease, are positioned ideally to provide the leadership to conduct a complex national trial involving a limited number of centers, perhaps under the auspices of an organization such as the American College of Surgeons Oncology Group.

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