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EDITORIAL – ENDOCRINE TUMORS

Peritoneal Metastases from Gastroenteropancreatic Neuroendocrine Tumors

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Dear Professor Balch,

We have read with interest the paper by Madani et al.[1] on peritoneal metastases (PM) from gastroenteropancreatic neuroendocrine tumors (GET-NETs) that was recently published in Annals of Surgical Oncology. While we acknowledge the valuable efforts the authors have made to further elucidate a topic that has not been given much attention in the existing body of the literature, we would like to express our concerns with regards to the data referring to the tumors arising from the appendix presented in this study.

The paper describes the experience of PM in a cohort of 4114 Dutch patients with GEP-NETs derived from the Netherlands Cancer Registry. The authors included in their cohort 953 patients with appendix NET (ANET), of whom 23 displayed metastasis to the peritoneum. Specifically, 10 patients had PM, and 13 had PM with additional metastases at other anatomical locations, while 10 had non-peritoneal metastases and 920 displayed no evidence of disease dissemination. Therefore, from this cohort, the reported incidence of PM in ANET is 23/953 (2.41%). Arguably, the most interesting conclusion in this subanalysis is the incredibly poor outcome of patients with ANET and PM (7% survival).

Although seemingly small, this rate of occurrence of PM in ANET is interesting in multiple regards. First, the rate of PM in GEP-NETs generally has hitherto been poorly categorized. Second, the management of ANET is highly contentious given their marked indolence compared with adenocarcinomas arising from the same location; there is considerable debate pertaining to the adequacy of appendectomy alone for disease control, which has a heavy focus on lymph node metastases. The oncological relevance of lymph node metastasis in ANET is questionable, and experience with PM from ANET is, at best, exquisitely rare.

Given the severely limited knowledge of PM in ANET, there are arguably two methods by which one may examine the experience of this clinical setting—review of case series of ANET, and published experience from peritoneal malignancy referral centers that may include such patients in their cohorts. The literature comes with the caveats of the rarity of ANET and changing histological nomenclature over time. In addition, tumors arising from the appendix encompass a very heterogeneous group of neoplasms, including appendiceal neuroendocrine tumors/neoplasms, mucinous carcinoids, malignant mucoceles, mixed exocrine-endocrine carcinomas (MANEC), and goblet cell carcinoids/carcinomas (GCCs) which were recently classified into three groups: typical GCC (Group A) and adenocarcinoma ex-GCC, which was further divided into signet ring cell type (Group B), and poorly differentiated adenocarcinoma type (Group C).[2] An accurate histological classification is pivotal for planning of treatment and estimation of prognosis since there is a significant variety of biological behavior among these tumor types.

Published case series of ANET rarely (if ever) describe the incidence of PM in this tumor type. In their study of 189 patients with 'well-differentiated endocrine carcinomas', Elias et al. describe only five patients with ANET and PM, which, in this study, were all associated with liver metastases.[3] In their earlier review of 116 patients with digestive endocrine tumors, Vasseur et al. did not identify any patients with appendiceal primaries, 11 of whom had peritoneal carcinomatosis.[4] More recent case studies applying modern histological classification criteria include that of Kleiman et al., which did not identify any incidence

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of peritoneal dissemination in their 78 patients.[5] We recently reported the largest non-registry surgical cohort of 215 patients with ANET treated at three tertiary referral centers, and while we documented a rate of lymph node metastases of 7.9% at the index appendectomy and 24.5% at the completion hemicolectomy, only two patients (<1%) had liver metastases and none had evidence of PM.[6] Of note, the 5- and 10-year overall survival rates in the entire cohort were both 99.05%. It is thus apparent from the literature that if the otherwise rare dissemination of ANET occurs, it is primarily to regional lymph nodes. Lastly, a recent systematic review, also by a similar team as the focus article, examined the impact on prognosis of appendiceal perforation in patients with appendiceal carcinoids, theoretically the likeliest source of peritoneal dissemination. Herein, of 103 patients with well-differentiated appendiceal carcinoids identified to have had perforation of the appendix, no incidences of peritoneal recurrence were observed.[7]

The experience of managing peritoneal malignancy with cytoreductive resection (CRS) and peritonectomy with hyperthermic intraperitoneal chemotherapy (HIPEC) has been reported in numerous large series ($n > 500$); however, these series, which include patients with appendiceal tumors, typically have neuroendocrine neoplasm histology as an explicit exclusion criterion, or only report epithelial tumors/mucinous adenocarcinomas.[8,9] Therefore, the presence of PM in ANET appears an incredibly unusual phenomenon.

Contrary to ANET, the proclivity of GCC of the appendix for peritoneal spread is much more widely appreciated. For example, in the large retrospective review by Lamarca et al. of 74 patients, 36% underwent CRS + HIPEC and 9% underwent CRS + HIPEC + adjuvant chemotherapy.[10] Such tumors display neuroendocrine features but must be clearly distinguished from the far more indolent ANET with rigorous immunohistopathological examination; however, this has not been widely recognized until relatively recently. Of note, the European Neuroendocrine Tumor Society no longer includes discussion of GCC in their current guidelines for ANET,[11] which was present in the previous iteration published in 2012.[12]

Pursuant to the aforementioned literature, the reported rate and outcomes of PM in ANET in this Dutch series must be scrutinized with the following questions:

(1) The veracity of histopathological classification is crucial in the diagnosis and management of appendiceal neoplasms. What histological criteria did the registry use to classify tumors as being ANET?
(2) Could GCCs and other more aggressive types of appendiceal neoplasms such as MANEC have been included in this study cohort and 'misclassified' as ANET?
(3) What were the clinicopathological characteristics of patients with PM in ANET in this series? Was there any indication of 'high-risk' features in these patients? (We note the Ki67 index was not available from the registry data.)
(4) Small ANET that are completely resected by appendectomy are often regarded as benign and may not be reported to cancer registries. Are all cases of ANET in The Netherlands included in the national registry? For example, Modlin and Sandor analyzed 8305 cases of carcinoid tumors recorded in various programs of the National Cancer Institute and the cases collected through the Surveillance, Epidemiology, and End Results (SEER) program.[13] They recommended that the results must be taken with caution because some of the programs included 'benign and malignant appendiceal carcinoids', while others focus on 'malignant appendiceal carcinoids' only.
(5) The 5-year survival of patients with appendiceal tumors and PM was 7% in this series. What was the overall 5-year survival in the entire cohort of patients with appendix as the primary tumor site?

We would like to thank the journal for giving us the opportunity to comment on this publication.

Sincerely
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