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COMMENTARY

A commentary on concurrent *MCL1* and *JUN* amplification in pseudomyxoma peritonei: a comprehensive genetic profiling and survival analysis

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Mucinous appendiceal tumors comprise of 1% of all colorectal cancer accounting for about 1500 cases per year in the United States.[1] These tumors originate in the appendix but often as a result of its growth within a narrow appendiceal lumen, the tumor perforates or may result in full thickness growth and invasion through the appendix lumen to involve the serosa. Transcoelomic seeding of tumor on the peritoneal surfaces result in the clinical syndrome of pseudomyxoma peritonei. Though this cancer is uncommon, there has been an enormous development in our understanding of the disease biology on the basis of its natural history in the last three decades. Dysplasia occurring in the mucus-secreting epithelium was initially classified histologically by Ronnett *et al.*[2] into three diagnostic categories comprising of disseminated peritoneal adenomucinosis, peritoneal mucinous carcinomatosis and an intermediate grade. This was based on the amount of cellularity, proliferative activity and presence of cytologic features of carcinoma. Today, the Bradley criteria is more commonly used and it dichotomizes the classification into a low- and high-grade group.[3] Surgical cytoreduction in combination with hyperthermic intraperitoneal chemotherapy has been demonstrated to be the standard of care achieving long-term survival gains over limited surgical debulking.[1] In a recent worldwide collaborative registry study, the 10-year survival of patients wherein a complete macroscopic surgical cytoreduction was not attempted or not possibly achieved operatively was $<10\%$ compared with that of $>70\%$ in patients who had a complete macroscopic cytoreduction.[4] Inability to achieve a complete cytoreduction may often be considered a surrogate reflection of an aggressive tumor that is more cellular and less mucinous resulting in more extensive invasion of the peritoneal surfaces. Patients with higher volume disease involving a larger extent of the peritoneal surfaces are also at higher risk of surgical morbidity. Further, recent data suggests a role for modern systemic chemotherapy in high-grade appendiceal tumors with radiographic responses demonstrated in 44% of patients.[5] If we were able to delineate molecular signatures and identify which tumors bear unfavorable tumor biology in addition to the current prognostic role of the histological classification, this may assist in treatment risk stratification. It will allow identification of suitable patients for surgical cytoreduction and/or for systemic chemotherapy. This would reduce surgical morbidity in patients who would otherwise not benefit from surgery.

Dr Sio and Miller *et al.*[6] from the Mayo Clinic performed exomic sequencing on paraffin-embedded tumor slides of 10 patients with pseudomyxoma peritonei. This is a landmark study although it included one patient with mucinous colorectal cancer (patient 2). This proof of concept study verified the potential feasibility of performing genetic profiling of pseudomyxoma peritonei where mutations were identified in 8 of 10 patients. Mutations identified include that of the *KRAS, GNAS, MCL 1* and *Jun* genes. Three patients had both *MCL 1* and *Jun* genes amplification and when survival trends were studied, the authors surmised that the presence of these amplifications demonstrated a slight trend favoring a prolonged survival. The authors should be congratulated on being the first group to report a study of genetic molecular profiling of appendiceal tumors. Some challenges of such study include the potential need to separate the mucin component of the tumor from the cellular component to ensure that sufficient volume of dysplastic cells undergo mutational analysis.

In future, when a larger cohort of patients is accrued, a more accurate mapping of gene mutations present in pseudomyxoma peritonei may be compiled and the identified genes of interest may then be further studied to define its prognostic significance. This may hopefully move towards a major step of being able to personalize surgical therapy in this disease. In turn, the genes identified may then lead to the development of a molecularly targeted agent for specific proteins as therapeutics that may be used in conjunction with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

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