Extrapancreatic malignancies and intraductal papillary mucinous neoplasms of the pancreas

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Abstract

Over the last two decades multiple studies have demonstrated an increased incidence of additional malignancies in patients with intraductal papillary mucinous neoplasms (IPMNs). Additional malignancies have been identified in 10%-52% of patients with IPMNs. The majority of these additional cancers occur before or concurrent with the diagnosis of IPMN. The gastrointestinal tract is most commonly involved in secondary malignancies, with benign colon polyps and colon cancer commonly seen in western countries and gastric cancer commonly seen in Asian countries. Other extrapancreatic malignancies associated with IPMNs include benign and malignant esophageal neoplasms, gastrointestinal stromal tumors, carcinoid tumors, hepatobiliary cancers, breast cancers, prostate cancers, and lung cancers. There is no clear etiology for the development of secondary malignancies in patients with IPMNs. Although population-based studies have shown different results from single institution studies regarding the exact incidence of additional primary cancers in IPMN patients, both have reached the same conclusion: there is a higher incidence of extrapancreatic malignancies in patients with IPMNs than in the general population. This finding has significant clinical implications for both the initial evaluation and the subsequent long-term follow-up of patients with IPMNs. If a patient has not had recent colonoscopy, this should be performed during the evaluation of a newly diagnosed IPMN. Upper endoscopy should be performed in patients from Asian countries or for those who present with symptoms suggestive of upper gastrointestinal disease. Routine screening studies (breast and prostate) should be carried out as currently recommended for patient's age both before and after the diagnosis of IPMN.

INTRODUCTION

After the initial description of intraductal papillary mucinous neoplasms (IPMN) in the 1980s and the World Health Organization classification in 1996, both the recognition and incidence of this potentially malignant neoplasm have increased. IPMNs have been extensively
studied and much has been learned about the radiographic findings, behavior and clinical management of these unique neoplasms[1-3].

In the last two decades, multiple reports have suggested that patients with IPMNs have an increased risk of developing extrapancreatic malignancies when compared with the general population. These malignancies may occur before, concurrent with, or after the initial diagnosis of IPMN with the majority of cases being diagnosed before or concurrently. The increased incidence of additional malignancies in patients with IPMNs influences the preoperative evaluation and long-term follow up of these patients.

This review will examine the current literature on this topic. Specifically, we will discuss the timing of additional malignancies and the possible mechanisms involved in the development of secondary malignancies. In addition, we will identify individuals with other malignancies who are at potential high-risk for the development of IPMNs and discuss the clinical implications of these findings with respect to the preoperative evaluation and long-term follow up of patients diagnosed with IPMNs.

ETIOLOGY AND RISK FACTORS FOR EXTRAPANCREATIC MALIGNANCY

There is no clear etiology for the development of secondary malignancies in patients with IPMNs. It is possible that the increased incidence can be attributed to increased surveillance at the time of diagnosis of IPMN. This is supported by the fact that a large number of patients are diagnosed with coincident extrapancreatic malignancies after an IPMN has been identified. The diagnosis of IPMN may prompt additional testing such as colonoscopy, esophagogastroduodenoscopy (EGD), or further imaging, leading to an increase in the diagnosis of extrapancreatic malignancies but not the true incidence.

Few factors have been consistently associated with secondary malignancies in patients with IPMN. Several studies have shown that the patients with IPMNs and extrapancreatic malignancies are older than patients with IPMNs and no extrapancreatic malignancies[4-8]. A multivariate logistic regression analysis using Surveillance, Epidemiology, and End Results (SEER) data demonstrated increasing odds of extrapancreatic malignancy before or at the time of diagnosis of IPMN with increasing age group. When compared to patients less than 45 years, patients 55 to 64 were 2.1 (95% CI: 1.2-3.7) times more likely to have an extrapancreatic malignancy at or before the time of presentation. Patients 64-74, 75-84 and 85 years and older were 3.1 (95% CI: 1.9-5.3), 4.0 (95% CI: 2.4-6.7), and 3.5 times (95% CI: 2.0-6.0) more likely, respectively, to have an extrapancreatic malignancy. Patients who were female and white also had an increased risk of extrapancreatic malignancy, before, concurrent with, or after their diagnosis of IPMN[9].

There are likely to be common genetic risk factors which are as yet unidentified. In a recent study evaluating the gene expression in IPMN[10], no difference was found in p53, p21, Bcl-2 and MUC5AC expression for IPMNs associated with or not associated with extrapancreatic malignances. However, the authors did note increased expression of the intestinal-type secretory mucin (MUC2) gene in the IPMN population with extrapancreatic neoplasms. Further evidence of genetic predisposition is suggested by a case report of IPMN associated with familial adenomatous polyposis (FAP). In this case a mutation in the second allele of the APC gene initially identified in the primary colonic tumor was also found in the pancreatic IPMN, implying a common genetic mechanism[11].

These genetic studies identify two potentially high risk groups. Based on their data, Lee et al[12] recommend more intense screening for extrapancreatic malignancy in patients whose IPMNs are MUC2 positive. In addition, patients with FAP may be at higher risk for development of IPMNs. Further studies are needed to make specific recommendations, although patients with FAP already undergo close surveillance. Identification of a pancreatic cystic lesion in this group should raise suspicion for IPMN especially in the setting of the identified mutation in the APC gene.

Patients with IPMNs may also share environmental risk factors for the development of extrapancreatic malignancies. Further genetic and environmental studies will be necessary to elucidate the etiology.

OVERVIEW OF PREVIOUS STUDIES

Sugiyama et al[13] in one of the first articles published about this topic, reported a 48% incidence of extrapancreatic malignancies in patients with IPMNs. Since then, nine additional studies have reported on the same topic. These studies are summarized in Table 1 including the total number of patients, frequency of extrapancreatic malignancies, percentage of patients with colon and gastric cancer, and the percentage of extrapancreatic malignancies occurring before or concurrent with the diagnosis of IPMN.

In the nine studies, the incidence of extrapancreatic malignancies ranged from 10% to 52%. In all studies the reported incidence of extrapancreatic malignancies exceeded the expected rate of such malignancies in the general population. With the exception of the study by Riall et al[13] all studies were single institution studies and included patients with both benign and malignant IPMNs. The Riall study was the only population based study and used data from the SEER Tumor Registry[14]. In addition, this study included patients with malignant (or invasive) IPMNs only, as benign IPMNs are not captured in SEER. Only three studies included patients that did not undergo surgery[7,11,14].

In all studies, the great majority of extrapancreatic neoplasms were diagnosed before or concurrent with the diagnosis of IPMN (range, 66%-94%). The Mayo Clinic study[14] did not evaluate the incidence of extrapancreatic malignancies after the diagnosis of IPMN. Each study
has varying lengths of follow up with a mean follow up between 14 and 50 mo after the diagnosis of IPMN. It is assumed that patients in all these studies are at the same increased risk for extrapancreatic malignancies after the diagnosis of IPMN. However, a low incidence is observed in some studies due to significantly shorter periods of follow-up after the diagnosis of IPMN. In addition, as half to one third of IPMNs in these reports are invasive, many patients go on to die from their IPMN-associated invasive cancer and therefore do not develop additional extrapancreatic malignancies.

**SITES OF EXTRAPANCREATIC MALIGNANCIES**

The digestive system is the most common site for secondary malignancies associated with IPMNs. The types of additional cancers reported in patients with IPMNs reflect cancer patterns in the country in which the study was done. Colorectal cancers were the most common extrapancreatic malignancies associated with IPMN in studies performed in Western populations, ranging from 3% to 12%6,13,14 while gastric cancers were reported in 6% to 15% of Asian patients with IPMNs4,6,8,11,12,15. The incidence of gastric cancers in Western studies was less than 1%6,13. Other GI malignancies reported in patients with IPMN include esophageal tumors, hepatobiliary tumors, carcinoid tumors, and gastrointestinal stromal tumors, although the rates are inconsistent among different studies. The Mayo Clinic group demonstrated a higher incidence of hepatobiliary (OR = 3.0, 95% CI: 1.1-8.1), esophageal (OR = 5.5, 95% CI: 1.8-16.5) and GI stromal tumors (OR = 3.8, 95% CI: 1.0-14.1) in patients with IPMNs when compared to a control population of patients referred to the Mayo Clinic. Lombardo et al13 also report a similar O/E ratio of 1.6 (95% CI: 0.8-3.4) for the development of colon cancer when the IPMN group was compared with the matched-control group from the general population, although this difference did not achieve statistical significance in their study.

For those tumors that arise outside the GI system, breast and lung cancers have been associated with an increased O/E ratio in IPMN patients when compared to the general population4,11. Prostate cancer, renal cell carcinoma, lymphoma, thyroid cancer, and other cancers have been reported in patients with IPMNs, but most of these tumors are present in only a small proportion of patients and no clear association with IPMNs has been established4,6,8,12,15.

In the Mayo Clinic study4,11, it was found that IPMNs were not only associated with malignant neoplasms but, as one might expect, they were also associated with a statistically significant increase in the incidence of benign neoplasms. These benign neoplasms are precursors for the development of future malignancies including adenomatous colon polyps and Barrett’s metaplasia of the esophagus. While they did not find a significant increased in colon cancer in IPMN, the incidence in colonic adenomas was significantly higher in patients with IPMNs than those with pancreatic ductal cancer (OR = 1.6, 95% CI: 1.2-2.3) or a control population from the Mayo Clinic (OR = 1.9, 95% CI: 1.4-2.4). A 21% prevalence of colon adenomas was also noted by Sugiyama and colleagues in their 1999 study14.

**DIFFERENCES IN POPULATION-BASED VS SINGLE INSTITUTION STUDIES**

All single institution studies were retrospective and had relatively small numbers of patients with IPMNs. From their design, retrospective studies are limited by the fact that complete data can be missed if history of prior cancer is not documented. In addition, follow up data are limited if patients go elsewhere for diagnosis and/or treatment of additional neoplasms that occur after the treatment of their IPMN. Moreover, it is conceivable that the
patients seen at a referral center differ from and undergo different treatment when compared to the general population. At a referral center such as Mayo Clinic, the number of patients treated for IPMN is high when compared with non-referral centers. Given the heightened awareness of the referral center, this may have prompted colonoscopy or further surveillance studies with closer follow-up, thereby increasing the observed prevalence of extrapancreatic malignancies relative to population-based studies. Furthermore, the many of single-institution reports include only patients undergoing surgery. It is possible that this population has a different incidence of extrapancreatic malignancies than all patients with IPMNs.

Population-based studies also have inherent limitations. The correct classification of IPMN relative to other cystic pancreatic neoplasms was unclear until 1996 when the World Health Organization defined clear criteria for its diagnosis. As such, many IPMNs may have been misclassified as pancreatic adenocarcinomas or other cystic neoplasms in population-based studies. The U.S. population-based study included patients from 1983-1991 only in order to follow all patients for ten years to determine the incidence of extrapancreatic malignancies after the diagnosis of IPMN and it is possible that many IPMNs are misclassified. In addition, this study included only invasive IPMNs since benign IPMNs (adenoma, borderline, or carcinoma-in-situ) are not registered in the SEER database. As such, this study could not evaluate the incidence in of extrapancreatic malignancies in benign IPMNs.

Regardless of their observed differences, all studies reached the same conclusion: there is an increased incidence of secondary malignancies in patients with IPMN when compared to the general population. This finding has significant implications in the management of patients with IPMNs.

**CLINICAL IMPLICATIONS**

The prognosis for patients with benign IPMNs is significantly better than for patients with invasive IPMNs, with 5-year survival rates of 60%-77% compared to 30%-50% [1-3]. As IPMNs (especially non-invasive) have a relatively favorable prognosis, associated extrapancreatic malignancies have potential prognostic significance. In patients who develop secondary malignancies, approximately 2% to 15% die from them [4,5,11,12].

Based on the literature, we recommend that a detailed personal and family history of previous cancers should be obtained when a patient presents with an IPMN. Given the increased risk of associated colonic neoplasms (either pre-malignant polyps or malignancy), a colonoscopy should be performed preoperatively if there is no history of colonoscopy in the ten years prior to diagnosis of IPMN. For patients in Asian countries or for those with history of upper gastrointestinal symptoms suggestive of gastric disease, an EGD should be obtained as part of the preoperative work-up. In addition, routine screening tests such as mammography for breast cancer, prostate specific antigen for prostate cancer, and digital rectal exam for prostate cancer should be up to date.

Data collected after the diagnosis of IPMN is made and therapy instituted are insufficient to develop systematic guidelines for surveillance for secondary malignancies in these patients. Because of the higher incidence of colonic neoplasia in patients with IPMNs, we recommend preoperative colonoscopy as described above. Based on the results of the preoperative colonoscopy, the current guidelines for colon cancer screening in patients with average risk should be followed. In patients older than 50 years, with a negative screening colonoscopy the guidelines for subsequent follow-up include: (1) fecal occult blood test or fecal immunochemical test every year, or (2) flexible sigmoidoscopy or multidetector computed tomographic colonography or double contrast barium enema every 5 years, or (3) rigid colonoscopy every 10 years after the age of 50 years if initial colonoscopy is negative [10]. There are no data regarding changes in the interval of routine screening tests for other malignancies such as breast and prostate cancer and screening for these malignancies should follow current national guidelines for the general population. Women should be screened for breast cancer with yearly clinical breast exam and mammograms after the age of 40 years. Men should undergo annual or biennial prostate specific antigen levels and digital rectal exam after the age of 50 years as recommended by the American Cancer Society.

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