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MINI REVIEW

Post-Metachronous Cancer of the Ampulla of Vater after Gastric Cancer Surgery: An Overview

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ABSTRACT

Post-metachronous ampulla of Vater carcinoma after gastric cancer is an extremely rare between multiple primary cancers. The published literature contains only a few cases. Among the cases males are found more frequently. The majority of the cases reported after early gastric cancer. The main problem is to distinguish between new cancer and metastasis in gastric cancer patients. Early onset of jaundice, which is the main clinical finding, is important in diagnosis. The main type of surgery is pancreaticoduodenectomy. In this study, the clinic, diagnosis, and treatment of the post-metachronal ampulla of Vater cancer and the highlights of management options reviewed.

Keywords: Ampulla of Vater, Cancer, Metachronous, Multiple Primary Neoplasms, Second Primary.

INTRODUCTION

Significant advances have been made in the diagnosis and treatment of malignant tumors. Despite this, the diagnosis of multiple primary cancers (MPC) is not new, and it was reported with a frequency of 4.7% in 1921, and this frequency is between 2-17% in epidemiological studies. MPC are defined by the criteria defined by Warren and Gates.[1] In this definition, cancers found in different organs, with different histology and without recurrence or metastasis are specified.[2-5] Later, the presence of more than one cancer at the same time was defined as synchronous cancer, and the detection of cancer in a different organ after the first cancer diagnosis was defined as metachronous by Moertel. The main problem is whether the lesion that occurs after anti-cancer treatment in a cancer patient is metastasis or a new cancer. MPC occur in different organs and have different histology and this situation is important in the differentiation of multifocal tumors or metastases. While the Surveillance, Epidemiology, End Results Program (SEER) database considers a 2-months time period to distinguish between synchronous and metachronous cancers, International Agency for Research on Cancer (IARC) specifies lesions with a diagnosis interval longer than 6 months as metachronous, have a histologically different type and are certain to have no metastasis.[6] The post-metachronous cancer of the ampulla of Vater is a rare entity after gastric cancer surgery.

Incidence and literature overview metachronous cancers are rarely seen after gastric cancer surgery. Lawniczak et al. detected 6.7% MPC in 862 gastric cancer cases in 2014, and 63% of them were metachronous lesions. In this series, 33.3% of cases were diagnosed after gastric cancer.[7] In the gastric cancer series of 4593 cases by Eom et al. from South Korea, the frequency of metachronous cancer was found to be 3.4%. Among 159 MPC, only 3 cases were bile duct cancer and none of them were post-metachronous cancers.[8] Kim JH et al. found 41 gastric cancer patients with MPC whereas without post-metachronous cancers of ampulla of Vater.[9] In another study, Park YK et al. reported the frequency of other primary cancers after gastrectomy as 18.4%. They found hepatobiliary system cancer in only 2 patients.[10] Ikeda *et al*. described 1070 patients with early gastric cancer and 5% of these patients had metachronous cancer.[11] It is frequently detected in colorectal, lung, kidney and liver of patients with gastric cancer.[12] In any of these series, metachronous cancers of ampulla of Vater was not detected. However, in recent years, case series have been published due to the increase in surveillance of gastric cancer patients. Early diagnosis of metachronous cancers may be effective in patients undergoing gastric cancer surgery with frequent control.[13] Although synchronous tumors are reported more frequently in patients with gastric cancer, metachronous cancers are less common.[14,15] To help comparison, the incidence of multiple cancers was 10%

among all cancers, while the frequency of multiple cancers in gastric cancer cases was between 1.7% and 8%, and in a series, the frequency of metachronous in gastric cancer cases was found to be 33.3%.[7] The incidence of metachronous cancers among MPC was found to be 58.5%.[9]

Epidemiology

The etiological factors in the formation of metachronous cancer are the host's genetic, hormonal, previous cancer diagnosis, alcohol and tobacco use, or environmental factors depending on the lifestyle.[9] While its association with breast, prostate, renal cell cancer and hemangioblastoma was shown in cancer predisposition syndromes, synchronous and metachronous cancers associated with polyposis coli in the gastrointestinal tract were reported.[16,17] In cancer patients, radiotherapy, chemotherapy, and clinical medical applications are sufficient to induce secondary cancers. In a series, metachronous tumors were seen in 17% of patients who received chemotherapy for gastric cancer.[7] However, there is evidence that sporadic cancer of the ampulla of Vater may also associated either synchronous or metachronous with other malignancies such as sporadic colorectal carcinomas.[18] Since the surveillance is longer in early stage gastric cancer patients, the incidence of metachronous cancers is higher.[19] For the occurrence rate of secondary tumors, the first peak is 4-5 years and the second peak is 10-12 years after the first operation.[20] A short interval is associated with a poor prognosis and a high risk of mortality. Metachronous cancers are prone to peritonitis carcinomatosis and have a shorter life expectancy than synchronous cancers.[21]

Pathology

The ampulla of Vater is a junction where intestinal, pancreatic duct and biliary cells are located together. Tumors developing in this region are divided into intestinal, pancreaticobiliary and mixed types, and pancreatobiliary type lesions are similar to pancreatic ductal adenocarcinoma. Detection of pancreatobiliary type histology has worse survival than the intestinal type.[22] The adenomatous polyposis coli (APC) gene mutation is found in the intestinal subgroup of ampulla of Vater cancer, whereas the pancreaticobiliary type has genes involved in pancreatic cancer such as Kirsten rat sarcoma viral oncogene homolog (KRAS), Tumor protein (TP53), and SMAD4.[23] Although the prognosis is poor if the stage of the primary tumor is advanced in MPC patients, the stage of metachronous cancer is important in determining the surveillance of the patient. Although deoxyribonucleic acid (DNA) mismatch has been detected in patients with gastric cancer and coexisting colorectal cancer. Whether the ampulla of Vater cancer occurs with the same carcinogenic mechanisms in gastric cancer patients or whether it develops independently that requires further investigation.

Clinical aspects

Cancer of the ampulla of Vater is a rare malignant tumor originating in the last centimeter of the common bile duct. While 45% of post-metachronous cancers were detected in routine controls, ampulla cancers were detected with clinical symptoms.[8] Patients present with symptoms related to biliary obstruction. Other symptoms, although less common, are upper gastrointestinal bleeding, pancreatitis, and unspecific abdominal pain. Compared with synchronous tumors, metachronous cancers are more common in women and younger ages.[7] Imaging tests may include ultrasound, endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography and computerized tomography are useful diagnostic methods.

Endoscopy plays a major role in the differential diagnosis of a bulging papilla as well as in the local staging of the disease.[24] Endoscopic ultrasound (EUS) guided-biopsies play a major role in the diagnostic accuracy.[25]

Cases

The first of the cases in the review was presented as a case report in the Japanese literature by Yoshizumi M et al. in 1968.[26] Ozeki *et al*. detected a cancer of the ampulla of Vater one year after the operation performed for gastric cancer in a 51-year-old patient.[27] In the other publication, a case report is a case of post-metachronous ampulla of Vater cancer that occurred 3 years later in a patient who was operated for early gastric cancer by Akiyama *et al*.[28] Since Akiyama also detected colon cancer in the case he reported, he recommended screening for biliary cancer in patients with polyposis coli and Gardner syndrome.The most comprehensive compilation of the coexistence of gastric cancer and post-metachronous cancer of the ampulla of Vater was reported by Eriguchi N *et al*. in 2001 he described only one metachronous cancer of the ampulla of Vater in a series of 5 MPC in their publication. This case underwent total gastrectomy+D2 for early gastric cancer, and

pancreaticoduodenectomy (PD) was performed for Stage 1 ampulla of Vater cancer 6 years later, and the patient died 2 years later. Eriguchi compiled 20 reports in which MPC was detected, of which only two were post-metachronous ampulla cancer.[29] (Table 1). Kim C. reported in his thesis that only one of the four bile duct cancers was post-metachronous. However, the characteristics of the case were not specified in the article.[30] The post-metachronous ampulla of Vater carcinoma was found more frequently in man than women.

The authors of this review describe a case that has not yet been published. The patient is a 54-year-old male who underwent hemigastrectomy and gastrojejunostomy for a gastric carcinoma located in the antrum in 2014. In the histopathological examination of the patient, he was diagnosed as a LN+28/52, poorly cohesive tumor located in the antrum, invading the subserosa, and tumour, nodes, metasis staging was found to be T3N3b M0. Calcium folinate + 5 FU was applied to the patient as an adjuvant treatment. Esophagogastroscopy and mitral regurgitation examinations were performed annually during the follow-up period of the patient. In December 2019, high bilirubin level was detected in the biochemistry tests of the patient.

A lesion with a diameterof 4 cm and dilatation of the intra and extrahepatic bile ducts were detected in the Magnetic Resonance Cholangio Pancreatography. A mass was detected in the head of the pancreas intraoperatively, and PD was performed. Pancreatobiliary adenocarcinoma was diagnosed by finding a tumor located in the ampulla of Vater (Figure 1), which caused almost complete obstruction in the common bile duct and invaded the common bile duct, pancreas, duodenum and peripancreatic tissue in histological examination. One year follow-up CT scan of the patient, there was no intra and extrahepatic bile duct dilatation and pathology of the tumor was not found. The patient died in 22 months after PD surgery due to multiple organ failure.

Figure 1: Tumor embedded in the ampulla of the biliary tract, with a resected surface (arrow).

Table 1: Clinicopathological features of post- metachronous cancer of the ampulla of Vater in the literature

Author (year)	Age/Sex	Type of Gastric Cancer	Interval Years	Operation Type	Pathology
Yoshizumi M et al. (1968)	46/M	Early Gastric Ca	4	Papillectomy	-
Ozeki Y et al. (1988)	51/F	Gastric Ca	1	PD	Moderately differentiated tubuler adenocarcinoma
Akiyama N et al. (2000)	62/F	Early gastric Ca	3	-	Well-moderately differentiated adenocarcinoma
Eriguchi N et al. (2001)	65/M	Early gastric Ca	6	PD	-
Yildirim M et al.(2021) *unpublished*	54/M	Gastric Ca	5	PD	Pancreatobiliary carcinoma

M: Male, F:Female, Ca:Cancer, PD: Pancreaticoduodenectomy

Treatment

The treatment of choice for ampulla of Vater cancer is papillectomy or resection according to majority of lesions.[31] It is generally agreed that complete surgical resection with negative tumor margins is the principal curative procedure for ampulla of Vater cancer.[32,33] Various surgical procedures that including endoscopic papillotomy may be considered for ampulla of Vater cancer. pT1 tumor, noninvasiveness, and the absence of high-grade dysplasia are Indications for endoscopic ampullectomy.[23,34,35]

However, endoscopic papillotomy is considered sufficient if the surgical margins are intact in the ampulla removed for diagnosis. The controversial issue is the incidence of metastasis in post- metachronous cancer of the ampulla of Vater at a rate of 8-45%. The rate of metastasis is higher in the pancreatobiliary type.[36] In selected cases, it is one of the interventions in surgical ampullectomy instead of PD because of its low morbidity and mortality.[37] The currently accepted surgical intervention is conventional or pyloric-sparing pancreaticoduodenectomy.[38] Five-year survival rate after surgical resection remains 70% for patients with ampullary carcinoma despite the improvements in operative techniques, and postoperative care.[39-41] However, we believe that the treatment option will be chosen according to the stage of the metachronous tumor as a result.

CONCLUSION

The post- metachronous cancer of the ampulla of Vater should be kept in mind as differential diagnosis when a tumor in the biliary tract is detected although it is extremely rare. The diagnostic workup of cancer of the ampulla of Vater is exactly the same as that advised for any other type of biliary neoplasia. These results suggest the importance of long-term follow-up for detection of post-metachronous carcinomas at sites other than the stomach for patients with gastric cancer.

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