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Review

Mixed Adenoneuroendocrine Carcinoma (MANEC) of the Gallbladder: A Systematic Review of Outcomes Following Surgical Management

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Abstract. *Background/Aim: Mixed adenoneuroendocrine carcinomas (MANEC) are uncommon tumors exhibiting both adenocarcinomatous and neuroendocrine differentiation. They most commonly arise in the colon, appendix, rectum or stomach, however, a limited number of MANECs have been reported to originate in the gallbladder (gMANEC). The aim of our systematic review was to accumulate the existing data on gMANEC with special attention to the clinicopathological characteristics, surgical approach, recurrence and survival rates of patients diagnosed with this rare malignancy. Materials and Methods: A comprehensive search of the literature was undertaken. Results: A total of 15 studies (14 case reports and 1 case series), which comprised 19 patients who successfully underwent surgical treatment for gMANEC were included in our systematic review. During a median follow-up of 8 months (range=2-48 months) the overall survival was 87% and the recurrence rate was 21%. Conclusion: Achievement of complete surgical resection is the mainstay of the therapeutic management. Additionally, the stage of the disease and the histopathological mapping of these tumors affect decision-making for adjuvant chemotherapy and seem to define the prognostic course of each patient.*

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Malignant tumors of the gallbladder are rarely encountered (1). Notwithstanding the fact that the gallbladder has a somewhat uncomplicated histological structure, a plethora of malignant lesions have been reported to arise from the gallbladder such as papillary and mucinous adenocarcinomas, squamous cell cancers, sarcomas and neuroendocrine tumors (1-4). Papillary adenocarcinoma is the most dominant histologic subtype accounting for approximately 98% of all gallbladder malignant tumors, while neuroendocrine tumors on the other hand are substantially uncommon accounting for a mere 0.5% (1, 5). Mixed adenoneuroendocrine carcinomas (MANEC) are even more rarely diagnosed tumors, which combine both adenocarcinomatous and neuroendocrine differentiation (6). The concept of MANEC was first officially introduced by the World Health Organization classification of tumors of the digestive system in 2010 (7). MANECs constitute a rather particular group of tumors characterized by great heterogeneity as the percentages of adenocarcinomatous and neuroendocrine differentiation may vary greatly yet according to their definition; presence of each component in at least 30% of the tumor is mandatory (Figure 1) (6).

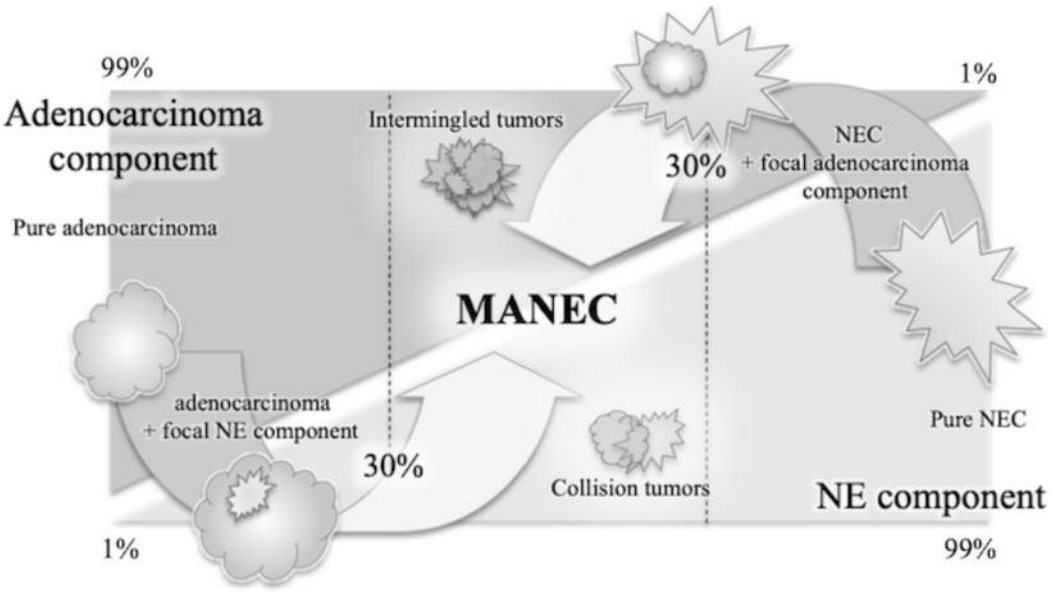

Figure 1. *Place of MANEC within the spectrum of adenocarcinomatous and neuroendocrine components.*

MANECs most commonly arise in the colon, appendix, rectum or stomach (8-11), however a limited number of MANECs have been reported to originate from the bile duct, the pancreas and the gallbladder (12-14).

Due to their rarity, outcomes of patients undergoing surgical management for gallbladder MANEC (gMANEC) remain ill determined. To that end the objective of our systematic review was to accumulate the existing evidence on gMANEC with special attention to the clinicopathological characteristics, surgical approach, recurrence and survival rates of patients diagnosed with this rare malignancy.

Materials and Methods

Study design. All appropriate observational studies and case reports, which addressed patients who were diagnosed with gMANEC and underwent surgical resection, were considered eligible for inclusion in our systematic review. Reviews and animal studies were excluded from analysis and tabulation. No language restrictions were applied.

Search strategy and data collection. A systematic search was performed for articles published up to June 2019 using the Medline, Scopus, and Google Scholar databases. The references within the retrieved articles were also retrieved in full text. The key words used for the search were the following: "gallbladder", "biliary tract", "MANEC", "mixed adenoneuroendocrine carcinoma", "composite adenoneuroendocrine carcinoma" and "combined adenoneuroendocrine carcinoma". In our attempt to assess an eligible number of studies that could be easily searched while simultaneously minimizing the potential loss of articles, a minimum number of search keywords were used. Articles fulfilling or deemed to fulfill the inclusion criteria were retrieved. All articles published from January 2000, which described patients aged >18 years who underwent surgical treatment for gMANEC were included. Data on patient characteristics included age and sex, while disease characteristics included primary symptoms, imaging studies performed to diagnose the lesions, administration and type of neoadjuvant treatment, type of surgery along with histopathological and immunochemical findings of the tumor. With regards to the main outcomes of the study, the follow-up period, mortality, administration of adjuvant treatment, and recurrence as well as survival rates were assessed.

Results

Included studies. A total of 15 studies (14 case reports and 1 case series), which comprised 19 patients who successfully underwent surgical treatment for gMANEC were considered eligible for inclusion and analysis in our systematic review as shown in Table I (14-28).

Main outcomes. The mean age of patients with gMANEC was 60±13 years, whereas the male to female ratio was 0.36 (5 male and 14 female). As reported by 15 studies, the majority of patients presented with epigastric or right upper quadrant (RUQ) pain (60%), while six (40%) were asymptomatic at the timing of diagnosis. Preoperative liver function tests were abnormal in five cases (15, 17, 20, 26, 28) while tumor markers were elevated in five patients (16, 17, 20, 26, 28). Preoperative imaging studies were used in 68.4% (n=13 out of 19) of cases. Ten patients (52.6%) had an abdominal computed tomography (CT), six (31.5%) had

Table I. *Patients and tumor characteristics*.

Author; Year	n	Age/ Gender	Primary symptom	Imaging studies	Neoadjuvant chemo	Treatment	Stage	CgA	SynA
Yannakou; 2001	1	72/F	Epigastric pain, nausea, weight loss	CT	No	RC	N/A	-	-
Shimizu; 2006	1	58/M	Epigastralgia	CT, angiography	No	Right hepatic trisegmentectomy	IVa	+	N/A
Oshiro; 2008	1	55/F	Back pain, fever, epigastralgia.	CT, ERCP, PET, MRI, MRCP, EUS	No	Pancreaticoduodenectomy, gallbladder, bile duct, and liver bed resection, LN dissection	IIIa	+	+
Sato; 2010	1	68/F	No	U/S, CT	No	RC, 4 and 5 liver segmentectomy	N/A	+	+
Chatterjee; 2014	1	73/F	No	CT	No	RC	I	+	+
Mondolfi; 2011	1	48/F	Epigastric RUQ pain	US, PET	No	Extended left lobectomy, partial right hepatectomy	N/A	+	+
Song; 2012	1	55/F	Epigastric pain	US, CT, PET	Yes	RC and LN dissection in hepatodudenal ligament and common hepatic artery	IIIa	+	+
Shintaku; 2013	1	80/M	No	N/A	No	RC	N/A	+	+
Abe; 2013	1	81/F	No	US, CT, MRI	No	RC	N/A	+	+
Meguro; 2014	1	54/F	Epigastric pain	CT, ERCP, MRCP	No	RC, Extrahepatic bile duct resection, LN dissection, and hepaticojejunostomy	II	+	+
Chen; 2014	1	34/M	RUQ pain	US, CT	No	RC and radical LN dissection	N/A	+	+
Acosta; 2015	1	55/F	Epigastric and RUQ pain	US	No	Robotic-assisted LC & Revision surgery	N/A	+	+
Azad; 2015	1	62/F	No	CT	No	RC	N/A	N/A	+
Kanetkar; 2018	1	77/F	N/A	N/A	Yes	RC	IIIb	N/A	N/A
	1	63/F	No	N/A	No	Revision RC	II	N/A	N/A
	1	50/M	N/A	N/A	No	Revision RC	II	N/A	N/A
	1	47/F	N/A	N/A	No	RC	IIIa	N/A	N/A
	1	64/F	N/A	N/A	No	RC	IIIb	N/A	N/A
Lin; 2018	1	43/F	RUQ pain	MRI	No	RC, partial liver resection, radical LN dissection	IIIa	+	+

n: Number of patients; CgA: chromogranin A; SynA: synaptophysin A; F: female; M: male; CT: computed tomography; ERCP: endoscopic retrograde choledochopancreatography, MRCP: magnetic resonance cholangiopancreatography; US: ultrasound; RC: radical cholecystectomy; LN: lymph node; RUQ: right upper quadrat; N/A: not available.

an abdominal ultrasound (US), three (15.7%) a positron emission tomography (PET) and three (15.7%) patients were diagnosed with magnetic resonance tomography (MRI), preoperatively.

Preoperative diagnosis of gallbladder carcinoma was established in six (31.5%) cases; in four of them preoperative biopsy was utilized (14, 17), while in the other four PET and endoscopic ultrasound (EUS) were used (26, 28). Considering the locally advanced stage of disease at the time of diagnosis, two patients (10.5%) received preoperative neoadjuvant chemotherapy with favorable response. One patient received carboplatin, paclitaxel, VP16 and octreotide for four cycles as a neoadjuvant chemotherapy and the other one received three cycles of carboplatin and etoposide (14, 17). All 19 patients underwent surgical resection; eight (42.1%) underwent radical cholecystectomy (RC), three (15.7%) patients had RC with lymph node dissection, two (10.5%) cases underwent revision RC, one had RC with extrahepatic bile duct resection and lymph node dissection, one (5.2%) had revision RC after robotic-assisted laparoscopic cholecystectomy, one patient underwent right hepatic trisegmentectomy (5.2%), one patient had pancreaticoduodenectomy, RC, bile duct resection and lymph node dissection (5.2%), one more had RC with segment IV and V liver resection (5.2%) and one (5.2%) patient underwent extended left hepatectomy. Immunohistochemistry staining analysis revealed positive expression of Chromogranin A (CgA) and Synaptophysin (SynA) in 92.3% of patients.

Long-term outcomes. Twelve studies reported long-term outcomes for 16 patients. Seven (36.8%) patients received adjuvant chemotherapy postoperatively. Five (71.4%) patients received carboplatin and etoposide for three cycles, one (14.2%) patient received three cycles of carboplatin, paclitaxel, VP16 and octreotide and one (14.2%) case received six cycles of cisplatin, etoposide and octreotide (14, 17, 24). Two patients refused to continue their treatment with

adjuvant chemotherapy postoperatively (20, 21). Two patients started intra-arterial chemotherapy and adjuvant chemotherapy after the presentation of recurrences (21, 28). During a median overall follow-up of eight months (range=2-48 months) the overall survival was 87%, whereas four (21%) patients reportedly presented with recurrence of disease within a median postoperative time of four months (range=2-11 months). Two patients died 2 and 3 months postoperatively due to disease progression.

Discussion

Mixed adenoneuroendocrine carcinomas of the gallbladder (gMANEC) are rather uncommon malignant tumors, whilst the vast majority of available data on these malignant lesions derive from case reports and small case series. Taking this limitation into account, our study group tried to collect all the available data in order to present the clinical features of the patients that suffer from gMANEC, the pre-operative imaging modalities used, as well as the possible diagnostic immunohistochemical markers, such as Synaptophysin (SynA) and Chromogranin A (CgA). In addition, we reported the therapeutic choices of gMANEC that have been recorded so far, including the pre-operative administration of neo-adjuvant chemotherapy, the type of surgical excision and the additional administration of adjuvant chemotherapy after surgery. Finally, we listed all the available outcomes of the patients that had undergone a surgical procedure due to gMANEC, including the disease-free survival rates, the overall survival rates, the possibility of recurrences and the cancer-related deaths.

The histopathogenic pathways of the evolution of mixed component tumors of the gallbladder remain hard to determine. One theory supports that the two distinctly different components may evolve in an independent fashion synchronously or metachronously or one component may metachronously derive from the other (16). Meanwhile, others support the hypothesis of both morphologically distinctive carcinomas arising from a common, multipotent stem or progenitor cell (16). As far as the histology of these rare tumors is concerned, interesting findings have been observed (8, 29). Features of ordinary adenocarcinoma are usually recognized in the tumor surface, the neuroendocrine component has been recognized in areas of vascular and perineural infiltration, while neuroendocrine components were prominent in lymph node involvement cases (29). In that setting, outcomes of preoperative biopsies of these lesions may be misleading as the neuroendocrine component is not easily or adequately recognized. Notably, it has also been observed that the neuroendocrine cancer (NEC) component may display higher proliferative activity than the adenocarcinomatous component, possibly implying that the neuroendocrine part (NEC) in biliary MANEC could dictate long-term outcomes in these patients (11, 29). As far as the immunohistochemical profile of these tumors is concerned, a minimum of two out of three regularly used markers, namely SynA, CgA and Cluster of Differentiation 56 (CD56), ought to be diffusely expressed to confirm the diagnosis of high-grade MANEC (30). In our study, both the expression of CgA and SynA were positive in 92.3% of patients.

It is acknowledged that long-term outcomes in these patients are largely dependent on the most aggressive component (adenocarcinoma/NEC) of their tumor (8, 31, 32). Long-term outcomes for patients with gallbladder neuroendocrine tumors have been shown to vary highly possibly due to their divergent disease stage and differentiation degree; 5-year survival rates range from approximately 37% to 60% (17, 33) whereas the addition of the adenocarinomatous component is thought to dictate worse prognosis.

The optimal treatment strategy for these tumors remains largely undetermined (6, 32). Notably, two of the included studies reported administration of neoadjuvant treatment resulting in successful resection of gMANEC in two patients initially deemed unresectable; one patient received carboplatin, paclitaxel, VP16 and octreotide for four cycles and the other one received three cycles of carboplatin and etoposide (14, 17). Such cases indicate that there may potentially be room in the future for administration of neoadjuvant treatment in selected patients with consequent beneficial outcomes, however, the currently available data to support such practice remain limited. Complete surgical resection (R0) should be pursued whenever possible and has been associated with improved survival rates (32). Surgical treatment of these tumors may range widely, and may range from simple cholecystectomy to minor hepatectomy with concomitant lymph node dissection and eventually extrahepatic bile duct resection depending on the extent of tumor invasion as assessed perioperatively. As a result of their heterogeneity and rarity, which lead to a failure to standardize chemotherapeutic regimens of choice, the efficacy of adjuvant chemotherapy is ill determined, however there is increasing data suggesting its efficacy in selected patients (34, 35). The choice of chemotherapeutic regimens to be used lies on the degree of MANEC differentiation and accordingly may follow a “treat-like-neuroendocrine tumor” or a “treat-like-an adenocarcinoma” protocol as suggested by previous investigators (32).

To the best of our knowledge this is the first systematic review to assess outcomes in patients with gMANEC who have undergone curative-intent resection. On the other hand, a number of limitations inherent to our study need to be addressed prior to reaching conclusions. Initially, the majority of the included studies were vastly restricted to case reports and a small case series not allowing further analysis of outcomes. Moreover, the retrospective nature of the included studies constitutes another limitation. Finally, another limitation is the significant heterogeneity among the

included studies, along with the fact that some critically important parameters, such as tumor differentiation, were not adequately presented.

Conclusion

The rarity of gMANEC remains the most significant obstacle in order to reach the most efficient standard practice. Nevertheless, the atypical clinical presentation of patients with symptoms or signs resembling cholecystitis should raise the suspicion of a malignant condition. Unfortunately, gMANEC is a histopathologic diagnosis, thus most of the times it is demonstrated post-operatively and confirmed by the expression of SynA and CgA. In cases where pre-operative diagnosis is feasible, for example with the utilization of EUS, neo-adjuvant chemotherapy seems to be beneficial for some patients. Complete surgical resection is the mainstay of therapeutic management. Additionally, the stage of the disease and the histopathological mapping of the lesion could affect decision-making for adjuvant chemotherapy, but ultimately these two elements seem to define the prognostic course of each patient. Consequently, in order to evaluate the optimal diagnostic and therapeutic strategies for gMANEC, the enlargement of the available literature and the design of further trials are required.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Conceptualization: NM; Literature search and analysis: AP, MF; Data extraction: AP, MF, VD; Table drafting: AP, MF, VD; Manuscript editing: NM, DM, DIT, DT, DS Critical revision ofthe manuscript for important intellectual content: NM, DS; All Authors have read and approved the final version of this manuscript.

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