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**Research Article**

# ROLE OF GENETIC MUTATIONS IN THE DIAGNOSIS OF GALLBLADDER NEOPLASMS

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**ABSTRACT**

Induction In Italy According to the most recent available epidemiological data, incidence rates for acute gallbladder cancer are 6.7 and 7.6 cases / 100,000 resident / year respectively in male and female populations; the mortality rate is 4,8 and 6,1 cases per 100,000 residents per year; 5-year survival is 21% in male and 18% in females, and then there is a series of crucial epigenetic alterations in biliary carcinogenesis. Due to the silent genes involved in a variety of functions, including apoptosis or growth arrest (p73, DAPK), DNA repair, and finding alterations in the DNA methylation pattern in the early stages of cancer carcinogenesis and even in chronic cholecystitis findings led to the hypothesis that modification of DNA The epigenetic structure is an early occurrence (18) This study shows the results of a research conducted on ca patients with the gallbladder using advanced diagnostics and gene expression precursors for the purpose of defining pre-clinical disease. Materials and Methods: From January 2015 to December 2017 at the AOU company in Catania, G Rodolico Presidium, the database was hospitalized in n 13 cases with gallbladder neoplasia, of which n 9 was female and 4 male with average age of 64 years Staging criteria are TNM AJCC in addition to headquarters and TN, the latter being the most important prognostic factor through determination of lymph node metastases, as well as invasion of the hepatoma ligament. Results Surgical resection is the only treatment that can offer a chance of treating cancer of the gallbladder. Surgical treatment depends on the stage of the neoplasm. Absolute resectivity criteria included the presence of liver, peritoneal and lymphoid metastases (in defined N2 stage - celiac lymph nodes, upper mesenteric artery, para-aortic and paracavals), neoplastic ascites, and widespread involvement of the peduncle liver The findings also confirmed the presence of gene mutations that may be one of the factors useful to assess the presence of neoplasia even at an early stage. Discussion Staging In patients with pT1b, pT2 and pT3 incident neoplasms, reintervention with hepatic resection, lymphadenectomy, resection of the cystic stump and in some cases VBP resection is now required. 2-3 cm of the liver bed and in patients with neoplasia In the case of cholecystitis neoplasia after cholecystectomy, cholecystectomy was sufficient in T1a and did not require reintervention as survival after simple cholecystectomy is close to 100 %. Thermoablation Used in localized localized control of small size (<3-4 cm in diameter), localized, non-resectable Conclusions in our brief experience determining genetic mutations helps to define the risk of neoplasia in the context of factors that determine the diagnosis . In the traditional model of cholangiocarcinogenesis, tumor promotion results in a background of cholestasis and / or chronic biliary flogosis: high cell turnover and abundant release of cytokines that facilitate the accumulation of mutations and the proliferation of genes with genetic alterations. the consequence of all this and that codetermination helps to define the clinical risk of neoplasia especially in the preclinical phase.



## INTRODUCTION

In Italy According to the most recent available epidemiological data, incidence rates for ca. of gallbladder are 6.7 and 7.6 cases per 100,000 resident / year respectively in male and female populations; the mortality rate is 4,8 and 6,1 cases per 100,000 residents per year; 5-year survival is 21% in male and 18% in females. The cumulative risk, ie the likelihood of getting sick

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during life, is about 1 out of 140. At the time of the 1990s, the incidence showed a decrease in the female sex, while in the male sex it did not undergo any variation beyond the statistical significance threshold. The risk stratification by age, almost zero up to the age of 40, from this age shows a steady increase in incidence, reaching the maximum age values over the age of 65. The most known risk factors for the Neoplasms are the presence of hepatobiliary parasites. The infection is caused by the ingestion of uncooked or raw fish, then the parasite colonizes the bile ducts and causes chronic inflammation, or chronic inflammatory phenomena and increased cell turnover. Recent risk factors for risk include cirrhosis, chronic B or C hepatitis, obesity, diabetes, and alcohol. The most common risk factor for gallbladder cancer remains biliary calculations or inflammatory processes that are present at diagnosis in most patients (75-90%). The risk is higher in subjects with large biliary calculus (greater than 3 cm calculations compared to those with <1 cm (1) and long-term cholelithiasis (in particular more than 40 years) (2). Gallbladder polyps are classified as bordeline or malignant lesions, and it is unclear whether adenomatous polyps represent precancerous lesions with the likelihood that they progress to carcinoma.3 Gallbladder polyps tend to not occur in patients with cholelithiasis, Chronic inflammation is generally absent and molecular cancer related changes seen in the cancer of the gallbladder have not been identified in adenomas.4 However, large polyps are more likely to contain invasive carcinomas and some studies suggest a correlation between the presence of gallbladder polyps and the risk of cancer of the gallbladder (5.6). In the Carcinogenesis Models The liver is a organ from regenerative capacity and has dual potential progenitor cells histopathological analysis and genetic profiling allow to identify two categories with mixed characteristics. In fact, depending on the degree of differentiation achieved prior to maturation arrest, heterogeneous phenotype can be observed. The alternative hypothesis for biliary cancer is the model of clonal evolution, a multistep tumor development process from precancerous lesions to invasive carcinoma, driven by the progressive accumulation of genetic and epigenetic alterations from a chronic inflammatory context (7,8). In chronic flogosis, the major cytokine involved in the inflammatory pathway to tumorigenis is IL-6, highly overexpressed in cell lines and found at high levels in cholangiocarcinoma samples. Membrane receptor binding (IL-6R) activates the Janus kinases (Jak1, Jak2, Tyk1), which phosphorylate transcription modulators such as STAT3. STAT3 phosphorylated dimerizes by composing a transcription factor that induces several genes including Mcl-1 that reduces cellular sensitivity to TRAIL mediated apoptotic mechanisms (9) Other mediators of cellular damage induced by chronic inflammatory disease are nitrogen monoxide ( NO) and cyclooxygenase 2 (COX-2). The latter inducible enzyme responsible for the conversion of arachidonic acid to prostaglandin H2, precursor to thromboxanes and other prostaglandins, is common inflammatory mediator in carcinogenesis of the gallbladder, expression of COX-2 is an early occurrence, p53 accumulation (10, 11). Oncogenesis can also occur in the absence of inflammation: through clonal evolution that is documented for the gall bladder cancer through a multi-step process that takes 10 to 15 years according to the hyperplasia or metaplasia sequence - dysplasia - in situ cancer - invasive carcinoma (12). The hypothesis is supported by the frequent finding of dysplastic areas close to gallbladder carcinomas (13) and the occurrence of similar genetic alterations in dysplastic and carcinogenic epithelium (14,15). For gallbladders carcinoma, a sequence of progression of the disease involving the adenoma - carcinoma transition (16) has also been described in a minority of cases. The mitogenic pathways are The second mechanism of carcinogenic cancer is the signaling pathways from the ErbB family receptors. Genetic alterations of EGFR (ErbB1), Her-2 / Neu (ErbB2) and some of their major transducers such as BRAF and KRAS have been described in some European studies. It should be noted that, in fact, the two inflammatory and mitogenic mechanisms are neither parallel nor clearly the other alternatives: their interrelation is intricate, with links at every level. Together with the proliferative stimulus, apoptotic evasion mechanisms in biliary cancer are called into question. , with a reduction in apoptotic events and the accumulation of further mutations, constitute a critical step in the cancerous pathogenesis of bile ducts. In carcinoma of the gallbladder, p53 loss is a frequently occurring stage during the early stages of nano-genesis and indeed also found in precancerous lesions (17). Then there is a series of crucial epigenetic alterations in biliary carcinogenesis, Due to The silenced genes involved in a variety of functions, including apoptosis or growth retardation (p73, DAPK), DNA repair, and the finding of alterations in the DNA methylation pattern in the early stages of cancer carcinogenesis, and even in findings of chronic cholecystitis, led to the hypothesis that modification of the epigenetic structure is an early event (18). Among the latest developments in preclinical research there is the demonstration of the role of expression of specific microRNAs (miRs), important mediators of post-transcriptional regulation of gene expression. The epithelium-mesenchymal transition is a key stage in the development of different tumors, the acquisition by carcinoma cells of an aggressive and dedifferenced phenotype, blast fibrous similar, is characterized by invasiveness and increased motility. Such cells lose epithelial markers (E-caderine and β-catenine that inhibit cell growth) and up-regulate mesenchymal markers such as N-cadherin, S100A4 and vimentin, related to in vitro invasiveness and poor prognosis in vivo (19,20). Another mechanism involved is the metalloproteases, proteins that degrade the extracellular matrix and promote cellular motility and invasiveness in cholangiocarcinoma, is their increased secretion, with a rise in MMP-7 and MMP-9 levels in Tumor samples (21,22,23) Even tumor stroma directly affects the natural history of the disease by producing several molecules associated with aspects of tumor progression (invasion, metastasis, differentiation, survival, lymphatic and perineural infiltration, vascularization alteration) according to well defined mechanisms involving specific receptor systems () (24,25,26,27). This study shows the results of a research conducted on ca patients with gallstones using advanced diagnostics and gene expression precursors for the purpose of defining pre-clinical disease.

## MATERIALS AND METHODS

from January 2015 to December 2017 at the AOU company in Catania, G Genoa, consulted in the database were hospitalized n 13 of cases suffering from neoplasm of the gallbladder, of which n 9 was female and n 4 was male with a mean age of 64 years. Clinical symptomatology was characterized by jaundice,

dizziness, weight loss, and graft pain, and in some patients the response was occasional and asymptomatic. There was no familiarity and in women there was prolonged use of estrogen in 62% of cases. the first diagnosis was conducted with the US Immunization Method, which has a diagnosis of tumor lesions in the gallbladder with a 88% sensitivity, 87% specificity, and a correct diagnosis rate of 87% though present limits such as: a) can not stagger the tumor completely, not displaying lymph nodes properly, peritoneal extension and remote metastases; b) does not exhibit pathognomonic signs especially in the initial stages where an unequal parietal thickening enters differential diagnosis, especially if thickening is extended. Subsequently, CT was staged, Fig. 2, as this method is able to demonstrate the neoplastic extension to the common bile duct bed and the surrounding liver, the presence of regional, peritoneal and remote lymphoid metastases. Angio-TC also documented the degree of vascular infiltration on the portal axis or liver artery, important elements during pre-surgical evaluation. In the diagnosis of carcinoma of the gallbladder, differential diagnosis and determination of the local extension of the tumor are important. For these purposes, prior to surgery, evaluation of tumor penetration within the gallbladder wall was essential to detect direct tumor invasion of other organs or the biliary system to determine whether there is a vascular invasion of major vessels, and evaluate the presence of lymph node metastasis or distance.

The diagnosis of stages I and II was provided by the finding in US fig 1 for the presence of localized or widespread nodular thickening of the gallstone wall or of a small solid formation adhering to the gall bladder walls or projecting in the lumen. In case of diffuse parietal thickening, differentiation with a cholecyptic aspect was based on the irregularity of the profiles and on the parietal thickness which generally exceeds 5-10 mm.

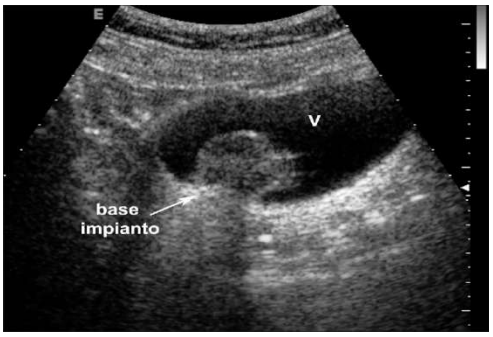


**Fig 1** US neoplasms gallbladder

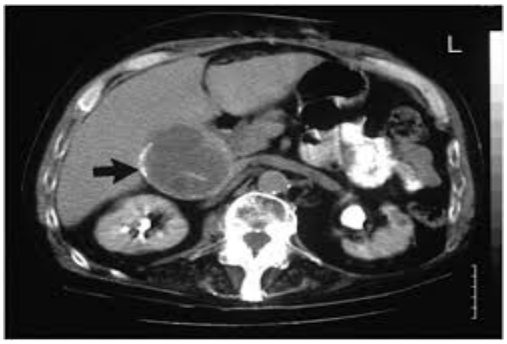


**Fig 2** TC neoplasms gallbladder

In the tumor of the gallbladder, the main imaging characteristics have been identified in focal or diffuse mastication; in the presence of an intraluminal polyposoid mass, usually> 2 cm, originating from the gallbladder wall. The RM provided useful information on the infiltration of the main biliary pathway and the endocoloric tumor extension and resilience

Factors that determined the resectability of the gallbladder tumor included the tumor stage according to the TNM AJCC staging criteria and the site and TN, the latter being the most important prognostic factor through the determination of lymph node metastases, invasion of the hepatoma ligand. All patients were subjected to chest CT. In Surgery A staging laparoscopy was performed prior to a laparotomy for a potentially healing resection when no remote metastasis was documented. For patients with jaundice (40% of cases), a cholangioRM was performed to evaluate liver and biliary invasion. PET was useful in detecting the presence of remote metastasis in patients with potentially resectable disease. Finally, a genetic study was associated to identify the mutations present on both flogic tissue and liquid biopsy.

## RESULTS

Surgical resection is the only treatment that can offer a chance of treating cancer of the gallbladder. Surgical treatment depends on the stage of the neoplasm. Absolute resectivity criteria included the presence of liver, peritoneal and lymphoid metastases (in defined N2 stage - celiac lymph nodes, upper mesenteric artery, near the-aortic and near the cava vein ), neoplastic ascites, and widespread involvement of the peduncle hepatic. Infiltration of the colon, duodenum or liver did not represent absolute contraindications. In the surgical approach in the resettable patient except for the patient with a colitis syndrome after cholecystectomy, in which the gallbladder has already been removed, present in our clinical observation in 15% of cases was based on removal complete with neoplasm with negative margins (R0). the main surgery was the hepatic resection of IVB-V segments with "en bloc" cholecystectomy performed in 70% of cases, but the extension of the resection can reach up to the right enlarged epatectomy with VBP resection in cases with multiple neoplasms extended, performed in 15% of cases. Liver resection was associated with resection of the cystic duct, the removal of the plaque, the regional lymphadenectomy including the liver lymph nodes (near the colic, near portal, near the artery), common liver artery to the celiac and tripododenal tripod. Lymphadenectomy plays a key role in the patient's staging. although it is related to a significant increase in operative risk. VBP resection was performed in the presence of a neoplastic infiltration along the cystic duct to obtain a R0 resection. In the case of cholecystoplasmic neoplasia following cholecystectomy histology, in T1a, cholecystectomy was sufficient and did not require reintervention as survival after simple cholecystectomy is close to 100% (44). However, before deciding not to intervene, it was necessary to acquire a series of data such as: whether complete cholecystectomy was performed, intraoperative bile loss. (with "bag"), histological examination, the state of the cystic retention margin, the histotype, the grading, and the presence of lymph nodes in order to determine if it was a tumor in situ (Tis) or a carcinoma pT1a, with the margin of the cystic neoplasia-free duct. In other cases, a treatment similar to that required in pT1b, pT2 and pT3 carcinomas was performed. 30-month follow-up after Stage I

surgical resection and occasional findings during cholecystectomy had a survival of 70%, respectively. In stage II of 15%. For the tumors that at the time of discovery infiltrated the musculoskeletal wall of the gallbladder (Stage III), the treated cases had a survival of 8%. Finally, for Stage IV, treated patients had a survival of less than 1 year. the genetic study of patients affected by this tumor subjected to the search for typical coding mutations was based on KRAS that analyzes DNA extracted from cells in 70% of cases, in INK4a in chromosome 9p21 (present in 52% of cases), in p53, which in most mutations were found in DNA binding domains (in 63% of cases), and in EGFR whose tumor mutations reside in specific gene portions (Exons 18,19,20,21) were present in 48% of cases. therefore, the results of these investigations confirmed that the presence of mutations can be one of the factors useful to assess the presence of neoplasia even at an early stage.

## DISCUSSION

Patient evaluation with a chest-abdomen TAC is the standard gold standard [28,29,30 31]. The RM, with the cholangiographic phase, seems to have greater accuracy to highlight the possible presence of a VBP invasion [32,33,24,25]. PET-TC does not seem to play an important role in considering the many false positives associated with pre- and post-operative flogic phenomena [36,37,38 39]. The role of "staging" exploratory laparoscopy is controversial. As some authors suggest that only patients with high risk of peritoneal carcinoma, ie those with poorly differentiated (G3), pT3 and positive margins (R1) after cholecystectomy [40,41,42,43], or with evidence of bile loss during cholecystectomy. and in order to predict the non-resectability of which the necessity in these cases is absolute. Intraoperative laparoscopic ultrasound increases the sensitivity and specificity of laparoscopy alone [44,45,46,47]. In relation to staging In patients with pT1b, pT2 and pT3 incident neoplasms, reintervention with liver resection, lymphadenectomy, resection of the cystic stump and in some cases VBP resection is required. Resuscitation of 2 -3 cm of the liver bed, and in patients with pT2 neoplasm which showed no lower recurrence and survival rate in the anatomy of the 4b / 5 segments [50]. however, it maintains its indication in pT3 tumors and in pT2 tumors located at the gall bladder level [48,49,50,51]. It should be noted that the thickness of 2-3 cm is to be maintained both at the bottom level and at the collar collar level and this could be technically more difficult than an anatomical resection of S4b and S5. in patients with suspected preoperative colitis cancer there is no laparoscopic cholecystectomy, and laparotomy cholecystectomy should be performed as confirmed by additional AA. Among the lesions of suspected gallbladder for neoplastic lesions are considered to be sessile and / or unique polyploid lesions, diameter $\geq$ 10 mm or showing rapid growth, The appearance of jaundice in a patient with cancer of the gallbladder has historically been considered a contraindication to the intervention in view of the worst prognosis [52]; only itteric patients without lymph node metastasis may benefit from a healing resection [53,54]. considered as Therapeutic approach of first-intention treatment The determinations of genetic mutations associated with the increase in cocaine 19-9 although these can be distorted by the presence of chronic inflammation can determine the risk of neoplasia present. In locally advanced disease RT was administered at a median dose of 56 Gy (range 36-52) on T and drainage lymph nodes when indicated, with T boost on reaching a median dose of 50 Gy (range 45-60). Concomitant chemotherapy was based on 5FU and gemcitabine. Overall no complete response to the treatment has been observed. Thermoablation includes radiofrequency ablation (RFA) Used in the local control of small lesions (<3-4 cm in diameter), localized, non-resettable, without extra-hepatic diffusion [55,56]. With 90-100% necrosis percentages. These results suggest survival benefits compared with other treatments. Arterial radiotherapy (TARE) consisting of intra-arterial infusion of radioactive substances, such as iodine-131 associated with lipiodol, or microspheres containing Ittrio-90 (90Y) through the liver artery (57,58). These arterial injected radioactive substances are released near the lesion, where they emit low penetrance and high energy (ß particles) radiation. TARE has proved to be a relatively safe procedure with minor side effects, most represented by asthenia, abdominal pain, and transient increases in serum bilirubinemia. It is to be considered as a valid alternative in the absence of extraepathic diffusion. Photodynamic therapy is relatively new for local treatment. It is an ablation method that involves intravenous injection of a photosensitizing drug followed by selective irradiation with light of a specific wavelength to initiate localized drug activation can significantly improve overall patient survival. preliminary results have not yet been confirmed.

## CONCLUSIONS

Combined approaches to chemio-radiotherapy or radiotherapy may be considered in non-resettable patients, but further clinical trials are needed to establish its effectiveness. in our brief experience, determining genetic mutations helps to define the risk of neoplasia in the context of the factors that determine the diagnosis. In the traditional model of cholangiocarcinogenesis, tumor promotion results in a background of cholestasis and / or chronic biliary flogosis: high cell turnover and abundant release of cytokines that facilitate the accumulation of mutations and the proliferation of genes with genetic alterations. the consequence of all this and that codetermination helps to define the clinical risk of neoplasia especially in the preclinical phase

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