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Abstract

The outcome of gallbladder carcinoma is poor, and the overall 5-year survival rate is less than 5%. In early-stage disease, a 5-year survival rate up to 75% can be achieved if stage-adjusted therapy is performed. There is wide geographic variability in the frequency of gallbladder carcinoma, which can only be explained by an interaction between genetic factors and their alteration. Gallstones and chronic cholecystitis are important risk factors in the formation of gallbladder malignancies. Factors such as chronic bacterial infection, primary sclerosing cholangitis, an anomalous junction of the pancreaticobiliary duct, and several types of gallbladder polyps are associated with a higher risk of gallbladder cancer. There is also an interesting correlation between risk factors and the histological type of cancer. However, despite theoretical risk factors, only a third of gallbladder carcinomas are recognized preoperatively. In most patients, the tumor is diagnosed by the pathologist after a routine cholecystectomy for a benign disease and is termed “incidental or occult gallbladder carcinoma” (IGBC). A cholecystectomy is performed frequently due to the minimal invasiveness of the laparoscopic technique. Therefore, the postoperative diagnosis of potentially curable early-stage disease is more frequent. A second radical re-resection to complete a radical cholecystectomy is required for several IGBCs. However, the literature and guidelines used in different countries differ regarding the radicality or T-stage criteria for performing a radical cholecystectomy. The NCCN guidelines and data from the German registry (GR), which records the largest number of incidental gallbladder carcinomas in Europe, indicate that carcinomas infiltrating the muscularis propria or beyond require radical surgery. According to GR data and current literature, a wedge resection with a combined dissection of the lymph nodes of the hepatoduodenal ligament is adequate for T1b and T2 carcinomas. The reason for a radical cholecystectomy after simple CE in a formally R0 situation is either occult invasion or hepatic spread with unknown lymphogenic dissemination. Unfortunately, there are diverse interpretations and practices regarding stage-adjusted therapy for gallbladder carcinoma. The current data suggest that more radical therapy is warranted.

Key words: Gallbladder carcinoma; Stage-adjusted therapy; Radical cholecystectomy; Gallbladder polyps; Gallbladder carcinoma: Prognostic factors and therapeutic options

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Cholecystitis; Gallstones; Laparoscopic cholecystectomy

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Core tip: The outcome of gallbladder carcinoma is poor. In patients with early-stage disease, a 5-year survival rate of 75% is possible. Stage-adjusted therapy is key for improving survival. Despite the theoretical risk factors of gallbladder malignancies, only a third of gallbladder carcinomas are recognized preoperatively, and radical re-resection in cases of incidental discoveries of incidental or occult gallbladder carcinomas is often crucial to complete a so called radical cholecystectomy. Unfortunately, there are diverse interpretations and practices regarding stage-adjusted therapy for gallbladder carcinoma patients. The current data suggest that more radical therapy is warranted.

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GENERAL DATA

Gallbladder carcinoma is the fifth most common neoplasm of the digestive tract and has an overall incidence of 3 per 100000 people. Gallbladder carcinoma is the most common cancer of the biliary tract[1]. A gallbladder carcinoma is found in 0.2%-3% of all cholecystectomies and 0.09%-2% of all laparoscopic cholecystectomies[2,3]. A gallbladder carcinoma is suspected preoperatively in only 30% of all patients[1]. The other 70% of cases are diagnosed using postoperative incidental findings by a pathologist. These cancers are termed incidental or occult gallbladder carcinomas. Only 15%-47% of the preoperatively known gallbladder carcinomas are suitable for resection[4]. The majority of symptomatic patients with malignant gallbladder disease have an incurable tumor. The outcome of gallbladder carcinoma is poor, and the overall 5-year survival rate is less than 5%. In early-stage disease, a 5-year survival rate of 75% can be achieved if stage-adjusted therapy is performed[5].

Gallbladder carcinoma is described in up to 3.4% of autopsies conducted on cholelithiasis patients over 60 years of age[6]. The risk of gallbladder carcinoma increases with age. There are 2 peaks observed in gallbladder tumor incidence. The first peak occurs at 50-60 years of age. The second peak occurs at 70-80 years of age and has a higher prevalence among women[7-9].

There is a wide geographic variance in the frequency of gallbladder carcinoma. The incidence rates are extraordinarily high in Mapuche Indians in Chile, South America. This population exhibits the highest rate of gallbladder cancer: 12.3/100000 for males and 27.3/100000 for females[10]. The women of north India have an incidence of 22/100000. In North American Indians (New Mexico) and Pakistan, the incidence is 11/100000. Europe has a low overall incidence of 0-4/100000. There are also relatively high rates observed in several Eastern European countries such as Poland, which has an incidence of 14/100000. The literature reports Japan as having a high incidence rate at 7/100000, though this value is low compared with that of Poland[11]. Epidemiological studies suggest that the mortality rates are related to the incidence. Countries with the highest incidence have the highest mortality rates. There is an inverse relationship regarding the cholecystectomy rate and incidence of gallbladder carcinoma. Thus, countries with a higher rate of cholecystectomy have a lower rate of gallbladder carcinomas because the patients with risk factors have their gallbladders removed before carcinoma develops. Therefore, a survey of disease risk factors is important.

RISK FACTORS

Gallstones represent an important risk factor in the formation of gallbladder malignancies. Concrements are present in up to 85% of patients with gallbladder carcinomas[12]. Furthermore, gallbladder cancer rates are correlated with the prevalence of gallstone disease[12]. Increasing stone size elevates the risk of developing gallbladder cancer. Gallstones larger than 3 cm are associated with a greater than tenfold increased risk of cancer compared with that of small gallstones[13,14]. The type of concrement also matters. Cholesterol gallstones resulting from a distinct local mucosal irritation and chronic inflammation are associated with a higher risk of cancer.

Chronic inflammation is strongly associated with the malignant transformation of cells. Chronic inflammation causes DNA damage, which provokes repeated tissue proliferation and restoration attempts. This response involves the release of cytokines and growth factors and, thus, predisposes cells to oncogenic transformation[15].

Chronic cholecystitis is typically caused by chronic irritation due to a cholelithiasis, which may produce cancer development after many years. Chronic inflammation can also result in calcium enclosure in the gallbladder wall. Only those with punctual calcium enclosures are considered premalignant, cases with transmural enclosures are associated with a decreased risk of carcinoma[16]. Porcelain gallbladder is a rare type of chronic inflammation that occurs in approximately 0.8% of all cholecystectomies and is associated with an increased carcinogenic risk. Porcelain gallbladder
is a form of diffuse transmural calcification. Several authors have reported a 62% carcinogenic risk, which appears to be an overestimation\[16\]. Additionally, xanthogranulomatous cholecystitis is associated with the development of gallbladder cancer but is not considered a precancerous lesion\[17\]. A prophylactic cholecystectomy is recommended for patients showing these particular disease patterns. The diagnosis is often based on postoperative findings. Chronic bacterial infection of the biliary tract is also a risk factor for biliary malignancy (e.g., Salmonella typhi, Paratyphi and Helicobacter bilis). The bacterial colonization causes the degradation of bile, chronic irritation, and inflammation of the biliary wall. These changes may affect malignant transformation by altering tumor suppressor genes or proto-oncogenes\[18,19\].

Primary sclerosing cholangitis (PSC) is a chronic inflammatory syndrome with a neoplastic “field effect” that further supports the role of chronic inflammation of the gallbladder and consecutive carcinogenesis as there is an increased rate of gallbladder tumors that occur via a metaplasia-dysplasia-carcinoma sequence\[20\]. The AASLD recommends an annual ultrasound to detect mass lesions in the gallbladder. A cholecystectomy is advised in patients found to have gallbladder mass lesions regardless of the lesion size\[21\]. According to the EASL, gallbladder mass lesions in PSC frequently (> 50%) represent adenocarcinomas regardless of their size. Therefore, a cholecystectomy is recommended in PSC patients with a gallbladder mass of even < 1 cm in diameter\[22\].

The association between environmental exposures and gallbladder cancer are unclear. The risk factors for gallstones and gallbladder carcinoma include obesity, metabolic syndrome, and diabetes. There is a risk of malignancy in diabetes mellitus patients in the absence of concrements in the organ\[23-27\]. An anomalous junction of the pancreaticobiliary duct is a congenital malformation that is rare in Western countries; however, the malformation occurs frequently in Asian populations and especially Japan\[28\]. The histological subtype is usually a papillary carcinoma. A prophylactic cholecystectomy is recommended for these patients.

When considering the risk factors for gallbladder cancer, it is important to assess the management of gallbladder polyps that are present in up to 5% of adults and are more frequently diagnosed due to better imaging modalities\[24,29\]. Approximately 60% of gallbladder polyps are cholesterol polyps and 25% have an adenomyosis with hyperplastic mucosa. An additional 10% of polyps are inflammatory polyps, and 4% of all gallbladder polyps harbor benign adenomas and have neoplastic potential\[30\]. It is not clear if benign adenomas progress to gallbladder carcinoma because the absence of adenomatous polyp residuum in gallbladder adenocarcinoma histology challenges an adenoma-carcinoma sequence. The following factors are signs of potential malignant growth: polyps greater than 10 mm, rapidly increasing polyps, solitary or sessile polyps, association with gallstones, patients over 50 years of age, and K-ras positivity. The S3 Guidelines\[31\] in Germany recommend a conventional cholecystectomy by laparotomy for polyps larger than 18 mm. Polyps > 5 mm warrant an endoscopic ultrasound. Observation via transabdominal ultrasound is recommended for polyps < 1 cm without additional risk factors. A laparoscopic cholecystectomy is recommended for polyps < 1 cm with risk factors or polyps > 1 cm independent of the presence of risk factors.

The worldwide variation in the prevalence of gallbladder cancer can only be explained by genetic factors and their alteration. One method of assessing possible environmental influences on the risk of developing gallbladder cancer is to examine changes in the cancer incidence after immigration events. First-generation immigrants in Sweden were studied by Hemminki et al\[32\] using the nationwide Swedish Family Cancer Database. Only women from India and Chile had an increased risk and Northern European immigrants showed decreased risks of developing gallbladder malignancies. The increased rate of gallbladder carcinomas in Chilean and Indian immigrants suggests that carcinogenesis susceptibility was present before emigration and was responsible for the cancer\[33\]. A study by Kim et al\[34\] identified potential markers of GBC. The close genetic similarity between early and advanced gallbladder carcinoma cases highlights the aggressive biology of early-stage gallbladder carcinomas\[34\].

Gallstones are one of the most important risk factors for developing cancer. The genetic alterations that occur in the gallbladder wall are important for understanding cancer development. The gallbladder wall is altered by gallstones. The molecular pathogenesis results in an accumulation of mutations that may lead to malignancy. The common genetic mutations responsible for carcinogenesis include the activation of oncogenes, deactivation of tumor suppressor genes, microsatellite instability, and methylation of gene promoter regions\[34\].

Several of these genetic changes are associated with particular risk factors. For example, cases with papillary carcinomas are 100% K-ras positive and K-ras is increased in cases of an anomalous pancreaticobiliary ductal junction. Squamous-cell carcinomas and adenocarcinomas are K-ras positive in 33% and 66% of cases, respectively. There was no detectable K-ras mutation in undifferentiated adenocarcinomas\[35\].

The genetic mutation profile is interesting in the context of chemotherapy for different histological types of gallbladder carcinomas. Papillary tumors are more responsive to EGFR tyrosine kinase inhibitors. Thus, EGFR targeted therapy could be an option. Adenocarcinoma histology carcinomas should be treated with gemcitabine and cisplatin. However, squamous-cell and adenosquamous-cell carcinoma are
not sensitive to chemotherapeutics. There is also an interesting correlation between risk factors and the histological cancer type. Approximately 80%-97% of gallbladder carcinomas are adenocarcinomas. The remaining 3%-20% of tumor types include squamous-cell, adenosquamous-cell carcinomas, or papillary carcinomas. Additionally, gallstones and sludge are coexistent in 96% of cases. There are gallstones present in nearly 100% of squamous-cell and adenosquamous-cell carcinomas. In particular, large (> 1.5 cm) cholesterin, composite, or combination gallstones were found more frequently in gallbladders with squamous-cell and adenosquamous-cell carcinomas. In nearly 88% of gallbladder adenocarcinoma cases, there are also gallstones present. In particular, large, cholesterin, composite, or combination gallstones (> 1.5 cm) have been found in 68.2% of adenocarcinomas. Furthermore, small cholesterin, mixed, or pigmented gallstones and biliary sludge are found in 31.8% of adenocarcinomas.

The association between gallstones and carcinoma in cases of SCC requires longer periods of time. Thus, the patients with SCC are often older. SCC is more locally aggressive and is less sensitive to chemotherapy. In locally advanced stages, the prognosis of SCC is worse than adenocarcinomas. However, it has also been shown that R0 resection of an intramucosal pure squamous-cell carcinoma has a comparable prognosis to adenocarcinomas. Papillary adenocarcinoma normally has K-ras mutations that are associated with pancreatobiliary reflux, but not with gallstones. Papillary adenocarcinoma patients are younger and have an abnormal pancreatico-choledochoductal junction, cystic duct dilatation, long common pancreatobiliary channel and adenomatous polyps. The patients are common in Eastern countries and Japan. Approximately one-third of gallbladder carcinomas are known preoperatively despite understanding the theoretic risk factors. In the majority of cases, the tumor is diagnosed by the pathologist after a routine cholecystectomy for a benign disease and these tumors are termed “incidental or occult gallbladder carcinomas”.

**SURGICAL APPROACH AND STAGE ADJUSTED THERAPY**

The gallbladder is currently removed laparoscopically in more than 75% of cases. In western countries such as Germany more than 90% of gallbladders are removed by the laparoscopic technique. However, the laparoscopic approach for treating gallbladder carcinoma remains controversial. In cases of preoperative suspicion, the laparoscopic approach is contraindicated for gallbladder carcinoma because of an increased risk of organ perforation due to grasping instruments, bile spillage, and port-site recurrences. Consequently, when GBC is suspected preoperatively, an open technique is recommended for performing a radical cholecystectomy. However, due to the minimally invasive nature of the laparoscopic technique, a cholecystectomy is performed more frequently. As a result, the postoperative diagnosis of early gallbladder carcinoma is more frequent. A second surgery for radical re-resection is required for IGBCs, depending on tumor stage. Several studies have suggested that laparoscopy for IGBC is associated with a greater risk of tumor dissemination than is the open approach. However, these conclusions are based on small sample sizes, inhomogeneous patient groups, and older data. Multiple studies including the GR, which has the largest number of IGBCs in Europe with more than 900 IGBC cases, indicated the primary access technique (laparoscopy vs the primary open technique) did not affect prognosis. A study by Cho et al. showed that the laparoscopic approach is feasible for suspected early-stage gallbladder carcinoma. However, stage-adjusted therapy should be performed regardless of the primary access technique.

Although there are guidelines in different countries, the literature, guidelines, and the compliance with those guidelines can vary for stage-adjusted therapy. Stage-adjusted therapy includes radical surgery of the liver and a lymphadenectomy. According to the S3 Guidelines in Germany, the recommended treatment for gallbladder carcinoma is liver resection in the form of wedge resection of the gallbladder bed or a resection of liver segments 4b and 5. This surgery is always combined with a lymphadenectomy of the hepatoduodenal ligament in cases of T2 and more advanced T-stages. A similar procedure is recommended even for T1b and more advanced carcinomas by the Guidelines of the National Comprehensive Cancer Network, which is an alliance of 25 of the world’s leading cancer centers.

The reason for a so called radical cholecystectomy after simple CE in a formally R0 situation is an occult invasion or hepatic spread, respectively a not known lymphogenic dissemination. A radical resection following R1 or R2 surgery should always be an individual decision based on the opinion of several surgical and oncologic specialists.

The types of liver invasion were described by Nagai et al. and include liver-bed and hepatic-tilar type. Ogura et al. further defined a gallbladder confined type, a liver bed type, and a hepatic-tilar type with an expansive and infiltrating pattern with continuous or discontinuous spread. Endo et al. described a venous and lymphogenic pathway of microscopic tumor cell seeding in the liver in T2 GBCs, which is a T-stage without direct infiltration in the liver. The use of venous drainage in the liver is well described by Boerma et al., in form of a drainage in portal system of both lobes of the liver and direct drainage in segments IV and V through so called vesicohepatic vessels.
Different modes of lymphatic spread were described by Fahim et al\(^\text{[6]}\) based on the anatomical work in fetuses of Clermont in 1909 and the 3 pathways described by Ito et al\(^\text{[5]}\) in adult cadavers. Shirai et al\(^\text{[6]}\) identified the regional lymphatic system of the gallbladder by intraoperative vital staining. Uesaka et al\(^\text{[59]}\) visualized the routes of lymphatic drainage in the gallbladder with a carbon particle suspension and found 3 different pathways. The final destination of all of the lymphatic routes is the confluence in the abdominal aortic nodes near the left vena renal location and the paraaortic nodes. Thus, preoperative knowledge regarding the paraaortic nodes is crucial if planning an ultraradical resection termed HD (hepato-pancreatic-duodenectomy) as shown by Sasaki et al\(^\text{[60]}\) or Kondo et al\(^\text{[61]}\). Kondo et al\(^\text{[62]}\) shows a combined (lymphatic and liver) mode of spread in GBC that could be subdivided into the following categories: a hepatic bed type, hepatic hilum type, bed and hilum type, lymph node type, cystic duct type and a localized type.

The T-stage that requires radical liver resection is still a matter of debate. The NCCN clinical practice guidelines in oncology recommend a liver resection and lymph node dissection in T1b and more advanced T-stages\(^\text{[53]}\). The literature\(^\text{[63-73]}\) supports radical GBC surgical therapy for the T1b stage and above. The German registry contains more than 900 IGB cases and supports radical resection for the T1b stage. The GR data highlight the importance of IRR in cases of T2 and T3 carcinomas\(^\text{[72,73]}\). The radical liver resection techniques are supported by evidence from the GR and the literature\(^\text{[74]}\). The data support a wedge-resection technique with respect to prognosis and preoperative morbidity in T1b and even T2 cases. The prognostic impact of positive lymph nodes in stage T1b to T3 incidental gallbladder\(^\text{[75]}\) and node dissection is important. The rate of positive nodes is 15.7% in T1b carcinomas, 46% in T2, and 75% in T3 GBCs.

Despite the many known risk factors, only 1/3 of all carcinomas are detected preoperatively. Less than half of these carcinomas are suitable for resection. Thus, it is important that the early-stage gallbladder carcinomas found in the 2/3 of patients who are diagnosed postoperatively as an incidental finding are treated with stage-adjusted therapy that includes liver resection and lymph node dissection.

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