Chapter 4

GALLBLADDER CANCER

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EPIDEMIOLOGY

The incidence of gallbladder cancer (GBC) varies according to countries and geographical locations. It's incidence is higher in East Asian countries and South America, mostly in Chile, besides in particular countries such as Pakistan India¹. However, GBC is the 6th most common tumor in Western countries, it is the most common gastrointestinal malignancy in Southwestern Native Americans and Mexican Americans^{2,3}. GBC incidence is 1 to 2 cases per 100,000 population in the United States but the incidence increases to 7.1 in 100,000 among Native American females with cholelithiasis, and 27.3 in 100,000 among Native Females in Chile^{4,5,3}. It is six times more common in women⁶. GBC incidence increases with age, and while it peaks in the 7th decade, there are studies suggesting that the incidence is increasing in young Americans^{3,7}.

ETIOLOGY & PATHOGENESIS

Although the pathogenesis of GBC has not been fully clarified, it is thought that gallstones, gallbladder infection, genetics, race, environmental factors, and socioeconomic level play a role in the occurrence of gallbladder cancer^{1,3,8}. The common feature of many etiological factors is that they cause chronic inflammation in the gallbladder³.

Gallbladder Polyps

Gallbladder polyps which are usually found at the gallbladder mucosa, in the pathological examination of cholecystectomy material or incidentally at abdominal imaging, originate from the gallbladder mucosa. Polyps may be benign or malign.

• Malign Polyps: Adenocarcinoma, Mucinous cystadenomas, Squamous cell carcinoma, Adenoacanthomas

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Table 2: The 8th edition of The American Joint Committee on Cancer (AJCC) Staging classification og gallbladder cancer			
Stage	Tumor	Node	Metastasis
0	Tis	N0	M0
1	T1	N0	M0
2a	T2a	N0	M0
2b	T2b	N0	M0
3a	Т3	N0	M0
3b	T1-3	N1	M0
4a	T4	N0-1	M0
4b	Any T	N2 Any N	M0 M1

Treatment

Curative treatment of GBC is particularly surgery. Extensive involvement of hepatoduodenal ligament or major vessels (Common hepatic artery, main portal vein) by the tumor, liver metastasis, extensive peritoneal metastasis, ascites, and paracaval, superior mesenteric artery, celiac artery lymph nodes metastasis are contraindications to resection³⁸. Cholecystectomy would be adequate for T1a tumors³⁹. For T1b, T2 tumors extended cholecystectomy, which is the removal of gallbladder and subsequently resection of adjacent at least 2 cm liver tissue adjacent to gallbladder bed (Segment IVb-V) should be performed⁴⁰. For T3 GBC, en bloc resection of gallbladder and adherent organs is an option but is not associated with improved survival⁴¹. T4 tumors are usually unresectable due to major vessel involvement. Radical resection of locoregional Lymph node (common bile duct, cystic duct, portal vein, or hepatic artery) metastasis is associated with improved five-year survival rates^{42,43}. However, existing lymph node metastasis beyond the locoregional lymph nodes is associated with poor survival rates⁴².

REFERENCES

- 1. Randi, G., Franceschi, S. & La Vecchia, C. Gallbladder cancer worldwide: Geographical distribution and risk factors. International Journal of Cancer, 2006; 118(7),1591-602.
- 2. Diehl, A. K. Epidemiology of gallbladder cancer: A synthesis of recent data. J. Natl. Cancer Inst, 1980; 65(6):1209-14.
- 3. Kelly, R. Haisley. John, G. Hunter. (2019). Brunicardi, F. Charles (ed). Schwatz's Principles of Surgery. (11th ed., pp 1393-1428). McGraw-Hill Education.
- 4. Carriaga, M. T. & Henson, D. E. Liver, gallbladder, extrahepatic bile ducts, and pancreas. Cancer, 1995;75(1):171-90.
- 5. Hundal, R. & Shaffer, E. A. Gallbladder cancer: Epidemiology and outcome. Clinical

- Epidemiology, 2014; 7(6):99-109.
- 6. Duffy, A. et al. Gallbladder cancer (GBC): 10-Year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). J. Surg. Oncol, 2008; 98(7):485-9.
- 7. Kiran, R. P., Pokala, N. & Dudrick, S. J. Incidence pattern and survival for gallbladder cancer over three decades An analysis of 10301 patients. Ann. Surg. Oncol, 2007;14(2):827-32.
- 8. Serra, I. et al. Risk factors for gallbladder cancer: An international collaborative case-control study. Cancer,1996;78(7):1515-7.
- 9. Wisam F Zakko, Salam F Zakko, MD, FACP, A. (2020). Gallbladder Polyps. Sanjiv Chopra, MD, MACP (Eds). Uptodate. Avaible at: https://www.uptodate.com/contents/gallbladder-polyps?search=gallbladder%20cancer&source=search_result&selectedTitle=5~57&usage_type=default&display_rank=5
- 10. Li, Y., Tejirian, T. & Craig Collins, J. Gallbladder polyps: Real or imagined? Am. Surg, 2018;84(10):1670-74.
- 11. Maria Farinon, A., Pacella, A. & Cetta, F. "Adenomatous Polyps of the Gallbladder." Adenomas of the Gallbladder. HPB Surg, 1991;3(4):251-258
- 12. Ishikawa, O. et al. The difference in malignancy between pedunculated and sessile polypoid lesions of the gallbladder. Am. J. Gastroenterol, 1989;84(11):1386-90.
- 13. Kubota, K. et al. How should polypoid lesions of the gallbladder be treated in the era of laparoscopic cholecystectomy? Surgery, 1995; 117(5):481-7.
- 14. Hsing, A. W. et al. Gallstones and the risk of biliary tract cancer: A population-based study in China. Br. J. Cancer, 2007; 97(11):1577-82.
- 15. Muszynska, C. et al. Predictors of incidental gallbladder cancer in patients undergoing cholecystectomy for benign gallbladder disease: Results from a population-based gallstone surgery registry. Surgery, 2017;162(2)
- 16. Bhoomi, M. (2020). Epidemiology, risk factors, clinical features and diagnosis. In Gallbladder Cancer. Kenneth, K Tanabe, MD. Christopher, G Willett, MD. (Eds). UpToDate. Avaible at: https://www.uptodate.com/contents/gallbladder-cancerepidemiology-risk-factors-clinical-featuresanddiagnosis?search=gallbladder%20 cancer&source=search_result&selectedTitle=1~57&usage_type=default&display_rank=1
- 17. Dan Huag, Joonki Lee, Nan Song, S. C. Cholecystectomy and the Risk of Hepatobiliary and Pancreatic Cancer. J Cancer Prev, 2020;30:164–172.
- 18. Appel, E. et al. Clinical Outcomes of Patients with Porcelain Gallbladder Diagnosed on CT. Acad. Radiol, 2020.
- 19. Chowdhury M, Khan A S, Karim R, Z. J. Porcelain Gallbladder:A Case report. Mymensingh Med J Jul, 2019;694–698.
- 20. Machado, N. O. Porcelain gallbladder: Decoding the malignant truth. Sultan Qaboos University Medical Journal, 2016; 16(4):416-421.
- 21. van Erp, L. W. et al. Risk of gallbladder cancer in patients with primary sclerosing cholangitis and radiographically detected gallbladder polyps. Liver Int, 2020; 40(2):382-392.
- 22. Karlsen, T. H., Folseraas, T., Thorburn, D. & Vesterhus, M. Primary sclerosing cholangitis a comprehensive review. Journal of Hepatology, 2017; 67(6):1298-1323.
- 23. Chijiiwa, K., Kimura, H. & Tanaka, M. Malignant potential of the gallbladder in patients with anomalous pancreaticobiliary ductal junction. The difference in risk between patients with and without choledochal cyst. Int. Surg, 1995;80(1):61-4.
- 24. Elnemr, A. et al. Anomalous pancreaticobiliary ductal junction without bile duct

General Surgery

- dilatation in gallbladder cancer. Hepatogastroenterology, 2001;48(38):382-6.
- 25. Dutta, U., Garg, P. K., Kumar, R. & Tandon, R. K. Typhoid carriers among patients with gallstones are at increased risk for carcinoma of the gallbladder. Am. J. Gastroenterol, 2000;95(3):784-7.
- 26. Kobayashi, T., Harada, K., Miwa, K. & Nakanuma, Y. Helicobacter genus DNA fragments are commonly detectable in bile from patients with extrahepatic biliary diseases and associated with their pathogenesis. Dig. Dis. Sci, 2005;50(5):862-7.
- 27. Li, Y., Zhang, J. & Ma, H. Chronic inflammation and gallbladder cancer. Cancer Letters, 2014;345(2):242-8.
- 28. Welzel, T. M. et al. Risk Factors for Intrahepatic and Extrahepatic Cholangiocarcinoma in the United States: A Population-Based Case-Control Study. Clin. Gastroenterol. Hepatol, 2007;5(10):1221-8.
- 29. Hanada, K. et al. Gene mutations of K-ras in gallbladder mucosae and gallbladder carcinoma with an anomalous junction of the pancreaticobiliary duct. Am. J. Gastroenterol, 1999 94(6):1638-42.
- 30. Hezel, A. F., Deshpande, V. & Zhu, A. X. Genetics of biliary tract cancers and emerging targeted therapies. Journal of Clinical Oncology, 2010; 28(21): 3531–3540.
- 31. Wistuba, I. I. et al. Allele-specific Mutations Involved in the Pathogenesis of Endemic Gallbladder Carcinoma in Chile. Cancer Res, 1995;55(12):2511-5.
- 32. Navarro, S. Eponyms in pancreatology: The people behind the names. Gastroenterol. Hepatol, 2017; 40(4):317-326.
- 33. Piehler, J. M. & Crichlow, R. W. Primary carcinoma of the gallbladder. Surgery Gynecology and Obstetrics, 1978;147(6):929-942.
- 34. John, S., Moyana, T., Shabana, W., Walsh, C. & McInnes, M. D. F. Gallbladder Cancer: Imaging Appearance and Pitfalls in Diagnosis. Canadian Association of Radiologists Journal, 2020;71(4): 448-458.
- 35. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2016;5:28-37.
- 36. Bang, S. H. et al. Differentiating between adenomyomatosis and gallbladder cancer: Revisiting a comparative study of high-resolution ultrasound, multidetector CT, and MR imaging. Korean J. Radiol, 2014;15(2): 226–234.
- 37. Singla, V. et al. Role of EUS-FNA for gallbladder mass lesions with biliary obstruction: a large single-center experience. Endosc. Int. Open, 2019;7(11):1403–1409.
- 38. Nishio, H. et al. Gallbladder cancer involving the extrahepatic bile duct is worthy of resection. Ann. Surg, 2011 253(5):953-60.
- 39. Wakai, T. et al. Early gallbladder carcinoma does not warrant radical resection. Br. J. Surg, 2001; 88(5):675-678.
- 40. Coburn, N. G., Cleary, S. P., Tan, J. C. C. & Law, C. H. L. Surgery for Gallbladder Cancer: A Population-Based Analysis. J. Am. Coll. Surg, 2008 207(3):371-82.
- 41. D'Angelica, M. et al. Analysis of the extent of resection for adenocarcinoma of the gallbladder. Ann. Surg. Oncol, 2009;16(4):806-16.
- 42. Chijiiwa, K. et al. Role of surgery for gallbladder carcinoma with special reference to lymph node metastasis and stage using western and Japanese classification systems. World J. Surg, 2000; 24(10):1271-6.
- 43. Yamamoto, M. et al. Surgical results of operations for carcinoma of the gallbladder. Hepatogastroenterology, 1999;46(27):1552-6.