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EDITORIAL

Is gall bladder cancer a bad cancer *per se*?

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Abstract

Gall bladder cancer (GBC) has one of the poorest outcomes of all cancers. Early GBC is difficult to diagnose on even computed tomography. GB has no submucosa and the cancer infiltrates directly into the muscularis propria. GB wall is thin and important adjacent organs viz. liver, duodenum and pancreas get easily infiltrated. Tumor in the GB neck often needs extended right hepatectomy. Infiltration of duodenum/pancreas may necessitate pancreato-duodenectomy or even hepato-pancreato-duodenectomy. Mortality of surgical procedures, when performed for GBC, is higher than when performed for other cancers. Survival in GBC, even after R0 resection, is poor. There is no proven role of neo-adjuvant or adjuvant therapy for loco-regionally advanced GBC. There is no role of palliative surgery in metastatic GBC. Early GBC is diagnosed incidentally after cholecystectomy for stones and requires reoperation for completion extended cholecystectomy but unfortunately, most surgeons are not aware of this. GBC has a peculiar epidemiology and is uncommon in the West and has, therefore, not received much attention. Preventive cholecystectomy for asymptomatic stones is not recommended and there is no serum marker for screening. With all factors pitched against it, it does appear that GBC is a bad cancer *per se*!

Key words: Gall bladder neoplasms; Cholangiocarcinoma; Cholecystectomy; Hepatectomy; Hepato-pancreato-duodenectomy

Core tip: Gall bladder (GB) wall is thin and important adjacent organs get easily infiltrated. Tumor in GB neck needs hepatectomy and infiltration of duodenum/pancreas necessitates pancreato-duodenectomy; mortality of these procedures is high. Survival in gall bladder cancer (GBC), even after R0 resection, is poor. There is no role of neo-adjuvant or adjuvant therapy. Early GBC, diagnosed incidentally after cholecystectomy for stones, requires reoperation but most surgeons are not aware of this. GBC, uncommon in the West, has not received much attention. Preventive cholecystectomy is not recommended and there is no marker for screening. GBC is a bad cancer *per se*!

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Gall bladder cancer (GBC), the commonest malignancy of the biliary tract, has one of the poorest outcomes of all cancers.

Early GBC has symptoms indistinguishable from gall stone disease (GSD). Diagnosis of early GBC is almost impossible on ultrasonography (US) and difficult on even computed tomography (CT) cf. hepato-cellular carcinoma (HCC) and peri-ampullary cancers; endoscopic ultrasonography (EUS) is better but is not available easily and everywhere. Magnetic resonance imaging (MRI) too has no role in the diagnosis of GBC (cf. cholangio-carcinoma). GBC is PET avid but its use is restricted mainly to detect spread than for diagnosis. Laparoscopy again is to look for peritoneal dissemination than for diagnosis.

Even the anatomy of the gall bladder (GB) is against it. Unlike the intestines, GB wall has no submucosa so that a mucosal cancer infiltrates directly into the muscularis propria. Normal GB wall is thin (< 3 mm) and important adjacent organs viz. liver, duodenum and pancreas get easily infiltrated. The hepatic surface of the GB has no peritoneal cover (serosa) so a GB tumor easily infiltrates the liver parenchyma. Surgical resection for GBC involves lymphadenectomy and one (liver) or more organs. A 2 cm liver margin is required for GBC (cf. colo-rectal cancer liver metastases CRLM where even 1 mm margin is acceptable). Liver resection is usually in the form of a wedge but a major liver resection may be required if there is significant liver infiltration. For tumors in the GB neck, CBD has to be resected to achieve a negative margin; right portal pedicle lies at a distance of just a few mm from the GB bed and has to be sacrificed to achieve a 2 cm liver margin thus needing extended right hepatectomy (ERH). Infiltration of duodenum/pancreas may necessitate pancreato-duodenectomy (PD) and some patients with loco-regionally advanced disease may even require hepato-pancreato-duodenectomy (HPD). Involvement of main portal vein and proper hepatic artery contraindicates resection. While minimally invasive surgery has been shown to be technically safe and oncologically adequate for several cancers, *e.g.*, esophagus, stomach and CRC, its role and place in GBC is yet to be established.

Mortality of surgical procedures for GBC is high; mortality of the same surgical procedures when performed for GBC is higher than when performed for other cancers, *e.g.*, mortality of major hepatectomy for GBC is 16% *vs* 4% for cholangio-carcinoma CC[1]. Mortality of HPD for GBC is much higher than that for CC[2]. In a recent review, the Nagoya group observed that HPD, which can be performed for CC remains controversial for GBC[3].

Survival in GBC, even after R0 resection, is poor. In many reports, no T3/T4 or node positive patient survived for 5 years. Even actuarial survival of GBC is much poorer, probably the poorest of all, than every other cancer - 5 year survival of stage Ⅲ GBC is 7%-8% cf. 72% for breast, 38%-74% for CRC and 9%-20% for stomach cancer in stage Ⅲ[4]. In many cancers, the survival curve plateaus after the first two years and very few late recurrences occur, *e.g.*, 5 year survival in CRC is 65% and drops to only 58% at 10 years[4]. In GBC, disease recurs and patients die even after five years; in a report of 165 patients with T3/T4 GBC, 25 patients survived for 5 years but only 11 survived for 10 years[5]. A critical review of major resections, *e.g.*, ERH, PD and HPD for GBC, reported mostly from Japanese centers, reveals that more patients died of these procedures than actually lived for 5 or 10 years because of them.

A large majority of GBCs are metastatic or loco-regionally advanced. In some cancers, *e.g.*, genito-urinary, breast and CRC, cure is possible even in presence of metastases; even repeat resections are indicated. In GBC, there is no role for resection in presence of metastases. Unlike some other cancers, *e.g.*, CRC and stomach, where the primary tumor should be resected for palliation even if metastases are unresectable, there is no role of palliative surgery in metastatic GBC. Total hepatectomy and transplant are options for unresectable HCC and CC and for neuro-endocrine tumors (NETs) with liver metastases but not for GBC. For loco-regionally advanced GBC, there is no proven neo-adjuvant treatment (cf. unresectable pancreatic, esophageal and rectal cancers). As opposed to breast cancer and CRC, where personalized chemotherapy is being increasingly used, the role of even adjuvant therapy is not well established in GBC. No molecular targets have so far been identified for GBC hence no biologicals are suitable for use.

GBC is resectable for cure only when it is confined to the GB and has spread to a few regional lymph nodes. Such early stage disease is invariably an incidental finding on histopathology of the GB removed for GSD. Most such patients need a reoperation for completion extended cholecystectomy (CEC)[6]; unfortunately, most surgeons are not aware of this and the patient is denied a possible attempt at cure. This is reflected in poor (50% for stage Ⅰ and 28% for stage Ⅱ) 5 year survival in more than 10000 patients treated between 1989 and 1996[4].

Injustice has been done to GBC as it was clubbed with liver in the 6th International Classification of Diseases ICD (1950), with other biliary cancers in the 7th ICD (1957) and with extra-hepatic bile duct and ampulla in the 8th ICD (1967); it was only in the 9th ICD (1977) that GBC received an identity of its own as 156 and recently as C 23.9 in the 10th ICD (2007).

The peculiar epidemiology of GBC is also its own enemy. GBC is a "non-western disease" - rare in United States/Canada, United Kingdom/Western Europe and Australia/New Zealand but common in Central/South America, Central/Eastern Europe, South Asia (India) and East Asia (Japan and South Korea)[7]. Not much funding is available and very little investigative work has, therefore, been done for GBC. Even rarer tumors, *e.g.*, cystic pancreatic neoplasms (CPN) and gastro-intestinal stromal tumors (GIST) have received more attention because of the populations they afflict. GBC is one of the few non-gender related cancers which are

more common in women than in men; in many under developed and developing economies, women tend to receive less optimal health care as compared to men.

Prevention, therefore, becomes important. Primary prevention remains a dream as the etiology of GBC is not yet known (cf. tobacco for lung and oral cavity, hepatitis for HCC). Secondary prevention, cholecystectomy for asymptomatic GSD, is invasive, expensive and risky and is not recommended. There is no serum marker (cf. PSA for prostate) for screening; surveillance of high risk groups viz. those with asymptomatic GS using US (cf. alfa-feto protein AFP for HCC in patients with cirrhosis or endoscopic, *e.g.*, for esophageal cancer in Barrett's and for CRC in inflammatory bowel disease IBD) is not an option as US detects the disease in advanced stage (Ⅱ or more) only.

With all factors pitched against it, it does appear that GBC is a bad cancer *per se*!

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