Need for Prophylactic Cholecystectomy in Silent Gall Stones in North India

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Abstract One of the criteria for recommending cholecystectomy for silent gall stones, is gall stones in regions with high incidence of gall bladder cancer. Both gall stones and gall bladder cancer are common in North India. All tertiary care centres in India report high rates of gall bladder cancer (GBC) incidence and poor treatment outcomes in the majority of cases due to advanced stage of presentation. Csendes of Chile has reported very high incidence of gallbladder cancer in Chile and Bolivia and advocated prophylactic cholecystectomy in asymptomatic patients. Incidence rate of gall bladder cancer in Indian males is equal to that of Chile, whereas in females, the rates are almost double the rates of Chile. Indians have also been found to have high concentrations of heavy metals in gall bladder wall, and antibodies to tumor suppressor genes. In India, gall bladder cancer is the commonest GI cancer in women and fourth commonest cancer overall in the female population. In view of the epidemiology and clinical scenario of gall bladder cancer and proven safety of laparoscopic cholecystectomy, there is a need to act before it is too late in the current rates of gall bladder cancer. This study looks at the evidence correlating gall stones and gall bladder cancer, in

relation to India. There is pressing evidence today to justify a strategy of prophylactic cholecystectomy in silent gall stones in North India. Data for this study was selected through an internet based search for literature concerning gall stones and gall bladder cancer in India, and for prophylactic cholecystectomy.

Keywords Gall bladder stones · Gall bladder cancer · India · Prophylactic cholecystectomy

Introduction

Asymptomatic gall stones are defined as stones that have not caused biliary colic or other biliary symptoms. Nearly two-third of patients with gall stones are asymptomatic.

The cumulative probability of developing biliary colic after 10 years ranges from 15 to 25 %. The incidence of other complications is much less. The operative mortality of elective cholecystectomy is less than 0.5 % but increased mortality is seen in elderly persons (>60 year of age), particularly in those with complications such as acute cholecystitis.

Most decision analysis studies till now have not favoured prophylactic cholecystectomy for asymptomatic cholelithiasis.

The indications for cholecystectomy in asymptomatic gall stones are as follows [1, 2]

- life expectancy >20 years
- calculi >3 cm or <3 mm in diameter,
- geographical regions with a high prevalence of gall bladder cancer
- presence of a chronically obliterated cystic duct
- non-functioning gallbladder or a calcified (porcelain) gallbladder
- women <60 years

Key Messages In view of the high incidence and poor treatment outcomes, of gall bladder cancer, there is pressing evidence today to justify a strategy of prophylactic cholecystectomy for silent gall stones in India. It is disturbing, that in spite of having nearly the highest rates of incidence of gall bladder cancer in the entire world, very little is being discussed about it in Indian literature. Over the long term this will help to reduce the chance of disease progression from silent gall stones to advanced gall bladder cancer.

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The following set of individuals will almost certainly benefit from pre emptive prophylactic cholecystectomy:

- Young adults and children because of higher cumulative lifetime risk of GBC.
- Those with thick GB walls, more than 3 mm, and half of them was xanthogranulomatous cholecystitis.
- Larger stones, more than 3 cm.
- Those with higher GB stone to GB volume ratios. Those with associated porcelain GB, large polyps, anomalous pancreatobiliary channels.

Those living in areas with higher incidence of GB cancer

The rationale for recommending a more aggressive approach for cholecystectomy in asymptomatic gall stones in India especially its northern parts, takes into consideration the following factors:

- Early onset of gall stone disease in women in India. Gall stones are the commonest associated risk factor with GBC, and occur at a younger age in India –the correlation is approximately 60 to 90 % which is statistically significant. Countries with low incidence of gallstones have low incidence of GB cancer. Larger stones and longer standing gall stones have been associated with more complications like Mirizzi's syndrome and xanthogranulomatous cholecystitis, and this has correlated with higher incidence of malignancy
- GB cancer is commoner here as compared to other parts of the world. In India too, it is more frequent in North and northeast India. It is actually the commonest GI cancer in women. Patients present late for treatment of GB cancer in India- the median duration of symptoms in India was 34 months in India, whereas it was 10 months in the UK. Also GBC often carries a poor prognosis in the stage at which it is detected in India today. GB cancer is the commonest cause of malignant obstructive jaundice in Lucknow, in North India [3]
- Laparoscopic cholecystectomy (LC) is a safe treatment strategy for gall stones, and many asymptomatic patients today will eventually need LC.
- A strategy of advising prophylactic cholecystectomy in patients with asymptomatic gall stones in areas with high incidence of GBC has worked elsewhere. Csendes of Chile recommended a strategy of prophylactic cholecystectomy in silent stones. University of Colombia validated this strategy. The annual age adjusted incidence rates in Chile is about 7 cases per 100,000 persons per year whereas the same rate for females in Kamrup, India is almost 14.
- The problem of high incidence of gall stones with a rising rate of GBC is a uniquely Indian problem. It has come to light in the last ten to fifteen years. There is a need for an

Indian strategy to be formulated timely for such a uniquely Indian problem.

- The widespread use of ultra sonography in the Indian health care set up offers the ability to pick up gall stones early in the disease. Since gall stones have a strong correlation with GBC, this offers an opportunity to treat the disease early, a blessing in disguise

Gallbladder Cancer- The Burden of the Disease in India

In a very significant publication Anu Behari et al [4], from SGPGI, Lucknow, India, have highlighted the following aspects of the disease-

- The highest rates of GBC are found in northern India and Pakistan, East Asia (Korea and Japan), Eastern Europe (Slovakia, Poland, and Czech Republic), and South America (Columbia and Chile).
- Incidence of GBC in women in northern India is as high as 9 per 100,000 per year as compared to, as low as 1 per 100,000, per year in parts of southern India.
- The risk of GBC increases with increasing size and number of gallstones, especially if the stones occupy a significant volume of the GB.
- Progressive changes in GB walls from chronic cholecystitis, hyperplasia, metaplasia, dysplasia, carcinoma in-situ, to invasive cancer over time have been reported from Chile. Based on these data, surgeons in Chile recommend prophylactic cholecystectomy in patients with gallstones – at the age of 30–40 years in women and 40–50 years in men.
- The incidence of GBC is also reported to be higher in patients with Xanthogranulomatous cholecystitis and Mirizzi's syndrome, both of which are associated with long-standing gallstone disease [3].

It is important to quantify the burden of GBC as a disease in India, and then compare it with the rates of incidence of GBC in other parts of the world before recommending prophylactic cholecystectomy. Murthy et al published the results of an extensive study in collaboration with Regional Cancer Center, Thiruvananthapuram, Kerala, India [5]. The article is an eye opener.

- In 1998–2006, incidence rates of gallbladder cancer (age-standardized rate, ASR) were high in Delhi and Kamrup (3.6 and 7.4) and (5.3 and 14.3) per 100,000 person years in males and females, respectively, and lowest in Aurangabad, 0.0 in both genders.
- An increased amount of fat or adipose tissue in an overweight or obese person probably influences the development of cancer by releasing several hormone-like factors,

or adipokines. These are pro inflammatory, and they promote pathological conditions like insulin resistance and cancer (Tables 1 and 2).

This alarming trend in the incidence of gall bladder cancer has caught the eye of a few other investigators in India. Mohandas et al from the Department of Digestive Disease and Clinical Nutrition, Tata Memorial hospital, Mumbai, India, found that many patients with GBC were women with substantial family responsibilities. A large majority of them were diagnosed to have advanced GBC, suitable only for palliation. They argued that a strong correlation existed between long standing gall stone disease and gall bladder cancer. Their contention is that prophylactic cholecystectomy should be offered to young healthy women from high-risk regions of India whenever they are diagnosed to have asymptomatic gallstones. Simultaneously, population-based observational studies may be started to generate more evidence [6].

In an attempt to determine why Indians have higher rates of GBC, a joint study from Lilavati Hospital, Mumbai, India and from Japan, looked at heavy metal concentrations in gall bladder walls removed from patients with gallstones and GBC. High concentrations of heavy metals in water and soil have been reported from North Indian cities. This Indo-Japan collaborative study compared presence of heavy metals in gallbladder tissues [7].

- Heavy metal concentrations were estimated in Indian GBC and cholecystitis tissues and compared with those in Japanese patients. Spectro photometry was done for 13 Indian gallbladder tissues (8 GBC, 5 cholecystitis) and 9 Japanese (5 GBC, 4 cholecystitis). Transmission electron microscopy (TEM) thin foil element analysis was done in 10 Indian samples (6 GBC, 4 cholecystitis).
- Chromium, lead, arsenic and zinc were significantly high in Indian GBC compared with Japanese GBC. Chromium, lead and arsenic were significantly high in the Indian cholecystitis tissues compared to the Japanese.

Table 2 ASIR (age specific incidence rate per 100,000 persons of gall bladder cancer in India (adapted from Curado et al, Cancer incidence in five continents, Volume IX, Lyon, France: International Agency for Research on cancer.2007.IARC Scientific Publication No 160

Age (years)	Chennai	Delhi	Mumbai	Nagpur
Males				
15–34	0.02	0.30	0.10	0.11
35–44	0.93	2.04	0.82	0.41
45–54	1.61	6.11	2.32	1.93
55–64	4.18	15.36	4.99	3.30
65+	4.45	22.08	10.66	2.91
Females				
15–34	0.09	0.71	0.19	0.05
35–44	0.60	5.99	1.79	0.65
45–54	1.50	19.64	3.93	2.69
55–64	3.37	30.52	7.89	2.56
65+	3.82	35.67	13.05	1.90

Another study looked at tumor suppressor genes like p 53 protein [8]. This study from North India found that about a third of the north Indian patients with GBC have antibodies to p53 protein. The commonest identifiable alteration in the p53 gene was a frame shift mutation at codon 271.

India has high rates of incidence of enteric fever and chronic salmonella carriers. Because of their chronic infection rates, such individuals have been found to have higher GBC incidence [9].

That GBC presents late for treatment makes the argument of looking for a prophylactic procedure stronger. A study from the All India Institute of Medical Sciences, New Delhi, India [10], looked at the records of more than 600 patients with GBC treated there, over a 10 year period. The investigators found that the large majority of patients had advanced disease at surgery. There were only six patients with stage I disease and 10 (3.4 %) patients with stage II disease, whereas 51 (17.5 %) patients had stage III disease, 137 (47 %) patients had stage IVa disease and 87 (29.8 %) patients had stage IVb GBC. Gallstones were present in 68 (49 %) of 139 patients in whom cholecystectomy (simple or radical) was performed. Their recommendation was that future studies should focus

Table 1 Age adjusted incidence rate of gall bladder cancer in Indian registries (ASIR – age standardized incidence rate)

Registry	Type of Registry	Period	ASIR per 100,000 males	ASIR per 100,000 females
Aurangabad	Urban	2001	0.0	0.0
Mumbai	Urban	2004–2005	1.6	2.6
Bhopal	Urban	2004–2005	2.3	4.3
Delhi	Urban	2004–2005	3.6	7.4
Kamrup urban district	Urban and rural	2005–2006	5.3	14.3

on early detection techniques and viable methods of mass screening, as only then can surgery be potentially curative.

A joint Indo Australian study published in the National Medical Journal of India [3], looks at the rates of GBC in various parts of the world (Table 3).

The inferences drawn from the study for GBC in India are:

- GBC incidence rates in India are considerably higher as compared to other parts of the world. It is possible that as a racial/ ethnic group, ‘Asian Indians’, like ‘American Indians’, are also at a higher risk for developing GBC in the presence of gall stones.
- Global trends for GBC reveal falling incidence rates, probably as a result of increasing rates of cholecystectomy for gall stone disease .
- Gall stone disease is common in north India and occurs at a younger age than in the western populations. It is the commonest gastrointestinal cancer in women. The incidence of gallbladder cancer parallels the prevalence of gall stone disease; large and long-standing gall stones being associated with a higher risk of gallbladder cancer.

Results and Discussion

The above data indicates that India, especially the area of the Gangetic plains, is possibly at the threshold of an epidemic of gall bladder stones and cancer. It is clear that at the present rates of detection, gall bladder cancer is being picked up late, and at an advanced stage where curative resection is not possible in the vast majority of cases.

The point is that it is still true that ‘*There is no innocent gallstone*’ (William J Mayo, MD, 1904)

The word “*asymptomatic gall stones*”, seems to be a misnomer in the sense it conveys an impression that the stones are

innocuous. However the fact is that gall stones have a statistically significant correlation with gall bladder cancer, and the strength of the relationship increases with higher stone size and volume. Northern India has also witnessed contamination of ground water sources with fertilizer and heavy metals. Heavy metals have been detected in high concentrations in gall bladder walls. This problem has come up only in the last ten to 15 years, and no other part of the world except perhaps some South American countries have witnessed similar high rates of GBC. They have responded by recommending prophylactic cholecystectomy in patients with silent gallstones. There is a need for a consensus meet to formulate a strategy to tackle this problem of rising gall bladder cancer in India. In view of the facts that ultrasonography is being used extensively in India, and even asymptomatic gallstones are often picked up, a strategy of advising cholecystectomy even without obvious history of biliary colic or dyspepsia, may be the answer to the problem.

The best recommendation in this context comes from a recent publication in 2012, from Behari, Anu, and V. K. Kapoor [11]. It states that “Till such data (concerning the rate of development of complications of gall stones) and evidence are available, surgeons and patients together would take a decision depending on their assessment of individual risks and choices. Patients definitely have to be cognizant partners in the decision after being explained the risks of waiting and an intervention that will not have any perceptible, immediate benefit, but has a definite risk of harm. There *MAY* be a case for suggesting preventive (for GBC) cholecystectomy in a young (20s or 30s) patient with a large GS in northern India but, as of today, there is no data or evidence to support it.”

The debate against cholecystectomy to reduce morbidity and mortality from GBC involves a cost benefit analysis. In a recent publication, Kapoor [12], looked carefully at this issue. A state in India like Uttar Pradesh, with a GBC prevalence rate of 4 % , and a population of approximately 200 million, should have about eight million patients. If one center were to perform five laparoscopic cholecystectomies daily over a 200 working day year, there would be a need for 800 such centers to work for 10 years to treat all patients with gall stones. With a 0.5 % risk of bile duct injury this could result in 40,000 bile duct injuries. Also the incidence of colonic cancer, duodeno gastric reflux and diarrhea has been reported to rise following LC. Also LC will offer no immediate clinical improvement when performed for an asymptomatic patient. But the prospect of saving eight million patients at the cost of 40,000 biliary strictures appears formidable but challenging as an option. And this equation assumes a prevalence rate of just 4 % whereas, in some areas like Delhi, prevalence have been reported to be higher than 10.

For appendicectomy, it is regarded acceptable, to have a 30 % rate of negative appendicectomy. The argument in favor of this approach is that if we were to wait for all patients with

Table 3 Abridged table showing age adjusted incidence of gall bladder cancer, 1983–87, per 100,000 persons per year. Source Parkin et al., Cancer Incidence in five continents. Vol VI. IARC Scientific Publications No 120. Lyon: IARC, 1992

Region/Country/City	Men	Women
West/Australia	0.8	1.4
West/Canada	0.7	1.4
West/United Kingdom	0.4	0.6
West/USA	0.6	1.0
South America/Argentina	4.7	4.2
South America/Bolivia	6.5	14.6
Europe/Hungary	1.6	5.9
Europe/Poland	2.4	7.1
Asia/Japan/Nagasaki	3.6	4.7

clinical suspicion of acute appendicitis to have the full blown picture, a large number of patients would develop complications. Why then, can the same argument not be applied to asymptomatic gall stones. By waiting for them to develop the full blown symptomatology, are we not increasing the stone exposure to the gall bladder wall, which we even today accept, is directly related to the risk of GBC. Or are we as Indian surgeons waiting for surgeons elsewhere to make tough decisions like this one for us?

Three studies have looked at the benefits of prophylactic cholecystectomy in gall stones in low risk populations and found that the benefits were irrelevant when compared to expectant treatment [13]. However in a personal communication, from Chile, a high risk population group, Puschel et al., reported significant benefit at a very low incremental cost [9].

Though LC to prevent GBC may not be acceptable in the western world where incidence of GBC is low, but in Northern India, where incidence rates are high it can offer significant secondary prevention [9]. One GBC could be prevented by performing only 67 cholecystectomies in high risk areas versus 769 cholecystectomies in low risk areas [14].

This study was conducted by means of an extensive internet based review of literature, published in the last 15 years using the key words gall bladder stone and gall bladder cancer.

References

1. Gupta SK, Shukla VK (2004) Silent gallstones: a therapeutic dilemma. *Trop Gastroenterol* 25(2):65–8
2. Patiño JF (1996) Suitability of laparoscopic cholecystectomy in the asymptomatic cholelithiasis patient. *Acta Gastroenterol Latinoam* 26(3):187–92
3. Kapoor VK, McMichael AJ (2003) Gallbladder cancer: an ‘Indian’ disease. *Natl Med J India* 16(4):209–13
4. Behari A, Kapoor VK (2010) Does gallbladder cancer divide India? *Indian J Gastroenterol* 29(1):9–13
5. Murthy N, Rajaram D, Gautham MS, Shivraj NS, Pruthvish S, George PS et al (2011) Trends in incidence of gall bladder cancer – Indian scenario. *Gastrointest Cancer: Targets Ther* 1:1–9
6. Mohandas KM, Patil PS (2006) Cholecystectomy for asymptomatic gallstones can reduce gall bladder cancer mortality in northern Indian women. *Indian J Gastroenterol*;25 (3)
7. Chhabra D, Oda K, Jagannath P, Utsunomiya H, Takekoshi S, Nimura Y (2012) Chronic heavy metal exposure and gallbladder cancer risk in India, a comparative study with Japan. *Asian Pac J Cancer Prev* 13(1):187–90
8. Nigam P, Misra U, Negi TS, Mittal B, Choudhuri G (2010) Alterations of p53 gene in gallbladder cancer patients of North India. *Trop Gastroenterol* 31(2):96–100
9. Lazcano-Ponce E, Miquel J, Muñoz N, Herrero R, Ferrecio C, Wistuba et al (2001) Epidemiology and molecular pathology of gallbladder cancer. *CA: Cancer J Clin* 51(6):349–364
10. Batra Y, Pal S, Dutta U, Desai P, Garg PK, Makharia G et al (2005) Gallbladder cancer in India: a dismal picture. *J Gastroenterol Hepatol* 20:309–314
11. Behari A, Kapoor VK (2012) Asymptomatic Gallstones (AsGS)–To Treat or Not to? *Indian J Surg* 74(1):4–12
12. Kapoor V (2006) Cholecystectomy in patients with asymptomatic gallstones to prevent gall bladder cancer–the case against. *Indian J Gastroenterol* 25(3):152–154
13. Sakorafas G, Milingos D, Peros G (2007) Asymptomatic cholelithiasis: is cholecystectomy really needed? A critical reappraisal 15 years after the introduction of laparoscopic cholecystectomy. *Dig Dis Sci* 52(5):1313–1325
14. Lowenfels AB (1985) Gallstones and risk of gallbladder cancer. *J Natl Cancer Inst* 75(1):77–80