# Feasibility of Using Trans Abdominal Sonography for Selective Screening for Gallbladder Malignancy in High-Risk Populations in Areas with Higher Incidence of Carcinoma Gallbladder in North India

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**Abstract**
*Problem*: Carcinoma Gallbladder is endemic in North India, with most cases presenting in advanced stages of the disease. Being relatively chemoresistant, detecting disease in the early operable stage is paramount for a cure. Screening in a large population in India is a formidable task, with a cost-benefit ratio of screening programs that must be carefully weighed for them to be practical and feasible. *Approach*: We explored the possibility of utilizing conventional Ultrasound as a screening test for carcinoma Gallbladder based on Wilson and Jungner's ten Principles of screening. We checked whether USG fulfils the ten criteria listed in classical work by Wilson and Jungner to qualify as a good screening test. *Finding*: We have found Ultrasound as an appropriate modality for screening gallbladder cancer in the high-risk North India population. It is cheap, readily available, acceptable to the population, and reproducible with no radiation hazard. It can also detect gallstones before they become symptomatic, which may help decrease the incidence of gallbladder cancer in the long term. *Conclusion:* In developing countries with a large population living in rural areas, cost-effective screening tests for Cancer are a formidable challenge. Our research convinced us that USG could be an effective modality for screening gallbladder cancer in India.

**Keywords:** Cancer, CT scan, Gallbladder, Gallstones, Screening, Ultrasound

## Introduction

Carcinoma Gallbladder (Ca GB) is a highly lethal malignancy with a 5-year survival rate of around 5% [1]. Several factors are responsible for this dismal outcome - Asymptomatic early phase, Late presentation, high Risk of distant metastasis, no precursor lesions, vague complaints overlapping with more benign problems like Acid peptic disease, and less effective systemic therapy. The burden of curative treatment lies with early diagnosis and the early institution of multidisciplinary treatment. With an increasing number of surgeons in India getting trained for complicated Oncologic Surgeries, increasing the survival rate of carcinoma Gallbladder patients further lies with early diagnosis and newer, more effective systemic treatment- hence the challenging part.

Carcinoma Gallbladder has a higher incidence in certain areas – Chile, parts of Europe, and India. In the Indian subcontinent, the incidence is higher in the Northern provinces than in the Southern provinces along the Gangetic belt, as mentioned in much literature from India [2]. However, it is unknown whether CaGB has any link to River Ganga or whether this association is just inferred from the fact that the Ganga river territory is vast, extending from Uttarakhand to Bengal, crossing four states [3-6].

Screening, per se, is not only recommended for any common disease, but a less common disease that has a higher impact on society due to poor outcomes also is fit for screening [7]. Ca GB fits this description.

Nevertheless, launching a screening program in a nation with more than 100 crore population and restrained resources is impractical, with a cost exceeding benefit. Any screening program planned for CaGB would be more cost-effective in northern India with endemicity for CaGB. Further narrowing down our list of target populations based on susceptible populations would increase the yield and cost-effectiveness of the screening program. Primary investigation for screening? Clinical examination, Ultrasound, CAT scan/MRI. Since the purpose of such screening/case finding is to diagnose early changes in the Gallbladder, the yield of clinical examination would be low as palpable lump and jaundice mostly signify advanced disease. Such screening cannot be a one-time event, so a CT scan may not be appropriate as a screening test due to radiation exposure, availability, and cost. A similar problem is with MRI- cost and availability. Transabdominal Ultrasound effectively visualizes the gall bladder – however, subjective variation and false positivity may be a problem.

Wilson and Jungner, in 1968 [8], elucidated Ten principles of screening in their landmark book "Principles and Practice of Screening for Disease," which still holds and is helpful while designing screening programs. In our study, we have analyzed whether screening of CaGB by Transabdominal Ultrasonography fulfils the ten Principles and whether screening/case finding by USG is feasible for CaGB.

**Methodology**

Wilson and Jungner elucidated Ten principles of screening as follows [8]:
1. The condition sought should be an essential health problem
2. The condition's natural history, including development from latent to declared disease, should be adequately understood.
3. There should be a recognizable latent or early symptomatic stage.
4. There should be a suitable test or examination.
5. The test should be acceptable to the population.
6. There should be an agreed policy on whom to treat as patients.
7. There should be an accepted treatment for patients with recognized diseases.
8. Facilities for diagnosis and treatment should be available.
9. The cost of case finding should be economically balanced concerning possible medical care expenditures.
10. Case finding should be a continuing process, not a "once and for all" project.

PUBMED/MEDLINE database was searched with keywords Gallbladder AND Carcinoma. Indian Council of Medical Research (ICMR) guidelines for CaGB were analyzed for epidemiological data of CaGB in the Indian Subcontinent.
The ten principles were studied and applied to CaGB and analyzed whether using ultrasonography as a screening tool fulfils the criteria and thus qualifies as a possible tool for CaGB screening in the high-risk population of Northern India.

**Result and Discussion**

1. The condition should be a critical Health problem.
Gallbladder Cancer has marked ethnic and geographical variations in incidence. It is prevalent worldwide in Chile, Europe, and the Indian subcontinent. Incidence in India, through available records, is around 10-22/100,000 [9]. Incidence in India is increasing, as evidenced by reports from ICMR-established cancer registries. However, there is a lack of a unified nationwide cancer registry. Hence, there is a high underreporting of cancer cases. There has been a recent ICMR initiative to establish more cancer registries across India [10]. Even a cancer registry may not reveal accurate incidence as most of the population lives

in rural areas and may not reach the tertiary hospitals for treatment where a cancer registry would be established. Underreporting is most notable for locally advanced inoperable and Metastatic cases.
Men are affected less than women, and North India has around ten times higher incidence of Gallbladder cancer than South Indians [11,12].
The disease has a very aggressive course. More than 50 % of cases have lymph node metastasis. Asymptomatic in the early phase, the disease usually presents in an advanced stage with few cases amenable to curative surgery. Chances of recurrence remain high even after curative surgery. There needs to be more effective systemic adjuvant therapy.

2. The condition's natural history, including development from latent to declared disease, should be adequately understood. 3. There should be a recognizable latent or early symptomatic stage. Unlike colon cancer, gallbladder cancer does not follow adenoma to carcinoma sequence. With no precursor lesion, there is a progression from dysplasia to carcinoma over several months to years [13].
Several factors are associated with a higher incidence of Gallbladder cancer. These factors may be targeted in screening programs with treatment recommendations based on the level of Risk. Gallstones (large size, solitary) [14], gallbladder polyps (large > 1 cm) [15], and porcelain gallbladder [16,17] are the most notable premalignant conditions. The earliest feature of gallbladder cancer usually starts with the thickening of the gallbladder epithelium, which later progresses to a mass that can partially or entirely replace the Gallbladder [18]. The purpose of any screening program for CaGB would be to recognize Cancer or suspect it at the thickening stage before it progresses to mass. That is the stage when it is most curable. According to TNM staging 2017, that would be T1b and T2. T1a is a microscopic tumour currently in use and not detectable by any radiological investigation. Segregating patients with the findings mentioned above may increase the yield of screening. However, certain benign conditions may mimic carcinoma-xanthogranulomatous cholecystitis and adenomyomatosis, thus contributing to false positives [19-20]. The Risk of having too many false positives is unnecessary surgery and anxiety due to the possibility of carcinoma. The solution lies in having a two-tiered screening program with a second tier of more sensitive and specific imaging for ruling out/ruling in carcinoma. CT scan/MRI / contrast USG may serve as second-tier tests.
Adenomyomatosis is often confused with carcinoma gallbladder. CT has limited sensitivity in differentiating between CaGB and Adenomyomatosis. HRUS and MRI have better sensitivity in differentiating both entities. Intramural echogenic foci on HRUSG are characteristic of adenomyomatosis. The presence of Intramural cysts on MRI/HRUSG is also an important feature [17-19].
Cholecystitis can mimic CaGB by the presence of thickening of the wall. Moreover, both may coexist (1-9%). A variant, Xanthogranulomatous cholecystitis (XGC), commonly confuses diagnoses due to its presentation and imaging findings similar to CaGB. On CT, hypodense nodules within the thickened wall are an essential feature of XGC. [20,21,22].
A few rare benign conditions may be confused with CaGB, and surgery is not required for them, but fortunately, as said, they are rare.
4. There should be a suitable test or examination.Owing to anatomical location, Ultrasound gives good anatomical detail about the Gallbladder, especially the fundus and body. Fortunately, the fundus and body are the most common sites of gallbladder cancer. Ultrasound, hence, qualifies to be a suitable screening test. HRUS can be a modality that can be used to decrease false positives. HRUS is accurate in diagnosing adenomyomatosis and cholecystitis (82%).
"Layered wall analysis" can accurately differentiate CaGB and other benign pathologies. A typical GB wall has an innermost hyperechoic layer of mucosa, a middle hypoechoic muscular layer, and an outermost hyperechoic peri muscular or sub-serosal layer. Any disruption of this pattern by CaGB can be easily detected by HRUSG [23].
In tier 1 investigation, transabdominal USG can be supplanted with HRUS if diagnostic confusion arises.With CT/MRI at the second tier, false positives can be further decreased, and it can be decided whom to operate and who should be kept under surveillance.

Ultrasound is operator-dependent. Hence, such screening should be done and recorded as per set guidelines. Such guidelines would be given to every participating radiologist. A short training program could also make them more familiar with these instructions. Such instructions would include the thickness of GB wall (present/absent), focal/generalized, maximum thickness in mm, layered analysis in HRUS examination, disruption in layer (present/absent), stones (present details), polyp[(solitary/multiple), size in mm], GB-liver interface. The radiologistAfter objective assessment, a radiologist shall generate his opinion as to whether the candidate is high Risk, low Risk, or indeterminate. All high-risk and indeterminate groups would be referred to the second-tier investigation centre.

5. The test should be acceptable to the population.
In the Indian subcontinent, where ultrasound centres are situated in every township in multiple numbers and being a relatively cheap, non-invasive test, USG qualifies as a test acceptable to the population. Ultrasound is already being used as a screening tool for any abdominal complaints.

6. There should be an agreed policy on whom to treat as patients.
Radiological signs of Gallbladder cancer- irregular thickening of the gallbladder wall, thickening of gallbladder wall more than 3 mm, mass replacing Gallbladder, and polyp more than 1 cm are the signs which, if detected, by screening would qualify a patient for second tier investigation – CT scan [18].
When to disclose the suspicion of Cancer? Any disclosure should be made after the second tier of investigation when treatment is to be planned.

7. There should be an accepted treatment for patients with recognized disease.
There is an accepted treatment protocol for gallbladder cancer. Worldwide, Extended cholecystectomy is the standard procedure recommended for operable gallbladder cancer [25]. Per NCCN guidelines, adjuvant chemotherapy/ chemoradiotherapy would be given in T2 or above and N+. The five-year survival rate for stage I gallbladder cancer is more than 90%, and stage II is more than 70% [25].

8. Facilities for diagnosis and treatment should be available.
There are many centres in Northern India treating patients with Gallbladder cancer. Owing to increased prevalence, many centres would qualify as high-volume centres for Gallbladder cancer, operating more than 20 cases yearly. Radiological investigations USG and CT scans are also readily available and cheap, especially in the government sector.

9. The cost of case finding should be economically balanced concerning possible medical care expenditures.
The cost of case finding is not appreciably high because a setup is already placed at various levels. As mentioned above, Ultrasound is cheap and readily available even at the trim township level. While tier 2 investigations would be planned at designated government hospitals, it is done at much cheaper rates than private setups, thus cutting the cost.

10. Case finding should be a continuing process, not a "once and for all" project.
Repeated screening annually would be needed. We propose a screening card akin to government IDs, which shall have all the information about the screening of that patient. It would include particulars, last date of screening, modality used, short report, tier 2 investigation if done, the result of any treatment recommendation, and the subsequent screening date. Software that shall have a complete database of all participants and send reminders to the individuals alerting them about upcoming screening dates may be developed. Screening would be voluntary; hence, camps educating the public, especially in rural areas, regarding the advantages of screening would be needed. This screening card may be used to screen for other cancers like breast, oral, and cervical Cancer.

## Conclusion

Gallbladder cancer seems to be an appropriate disease to have a dedicated screening program in Northern India. The aggressive nature, defined treatment, and possibility of early-stage cure make the Gallbladder amenable to screening and adopting the "Search and Destroy" approach. Critical appraisal of using USG as a screening modality for Ca Gallbladder may suggest that it could increase the number of cholecystectomies and, hence, associated complications- most notably, biliary injury. However, if we look at the development of cholecystectomies in the past decade, surgery has become safer with decreased biliary tract injuries.

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