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# Ultrasound surveillance for cholangiocarcinoma in an endemic area: A prove of survival benefits.

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## Abstract

**BACKGROUND AND AIM:** Cholangiocarcinoma (CCA) is an aggressive malignancy with rapid progression and poor prognosis. Abdominal ultrasound surveillance may detect early-stage malignancy and improve surgical outcome. However, little data exist on the benefits of abdominal ultrasound surveillance in populations at high risk for CCA development in an endemic area. This study compared survival outcomes of CCA patients recruited through abdominal ultrasound surveillance program and those presented to the hospital independent of surveillance.

**METHODS:** The surveillance population-based cohort was 4225 villagers in Northern Thailand, aged 30-60 years, who consented to a 5-year abdominal ultrasound surveillance program, which included interval ultrasound examinations every 6 months. The non-surveillance cohort was hospital-based CCA patients diagnosed during April 2007 to November 2015. Numbers of operable tumors, percentages of R0 resection, and survival analyses were compared between the two cohorts.

**RESULTS:** There were 48 and 192 CCA patients in the surveillance and the non-surveillance cohorts, respectively. Of these, 37/48 (77.1%) and 22/192 (11.5%) were in an operable stage and R0 resections performed in 36/48 (97.3%) and 14/192 (63.6%), respectively. The median survival in each group was 31.8 and 6.7 months, respectively (with correction of lead time bias) ($P < 0.0001$). By multivariate analysis, abdominal ultrasound surveillance (hazard ratio [HR] = 0.41; $P = 0.012$), operable stage (HR = 0.11; $P < 0.001$), and serum albumin ≥ 3.5 g/dL (HR = 0.42; $P < 0.001$) were significantly associated with decreased mortality, whereas size of CCA (HR = 1.11; $P < 0.001$), serum alanine aminotransferase > 40 IU/L (HR = 1.71; $P = 0.017$), and tumor recurrence (HR = 4.86; $P = 0.017$) were associated with increased mortality.

**CONCLUSION:** Abdominal ultrasound surveillance provided survival benefits and should be considered in areas highly endemic for CCA to reduce mortality.



**KEYWORDS:** biliary neoplasms; cholangiocarcinoma; epidemiology; liver tumors; malignant (non-HCC)

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# Ultrasound Surveillance for Cholangiocarcinoma in an Endemic Area Provided Survival Benefit

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## Abstract

**Background and Objective:** Cholangiocarcinoma (CCA) is an aggressive malignancy with rapid progression and poor prognosis. Abdominal ultrasound surveillance may detect early-stage malignancy and improve surgical outcomes. However, data are limited on the benefit of ultrasound surveillance in populations at high risk for CCA. Thus, this study aimed to compare survival

outcomes of CCA patients who were detected in an ultrasound surveillance program with those who presented to hospital independent of surveillance.

**Methods:** Two cohorts were included. The non-surveillance cohort consisted of patients with CCA who presented to and received treatment during April 2007-November 2015. The surveillance cohort was participating in the 5-year, ultrasound surveillance program in Nan Province, northern Thailand. The 4,225 participants were aged 30-60 years, with interval abdominal ultrasound examinations every 6 months. Numbers of operable tumors, percentages of R0 resection, and survival analyses were compared between these two cohorts.

**Results:** 192 and 48 patients were in the non-surveillance and the surveillance cohorts, respectively. Of these, 22/192(11.5%) and 37/48(77.1%) were in the operable stage and subsequently received R0 resections in 14(63.6%) and 36(97.3%), respectively. Median survivals in the two groups were 6.7vs 38.2 months, respectively (P<0.0001). From multivariate analysis, receipt of ultrasound surveillance (HR=0.41; p=0.012), operable stage (HR=0.11; p<0.001), and albumin level (HR=0.39; p<0.001) were significantly associated with decreased mortality. Whereas, size of CCA (HR=1.09; p=0.001), and tumor recurrence (HR=3.87; p=0.036) were associated with increased mortality.

**Conclusion:** Ultrasound surveillance provided survival benefit and should be considered in areas highly endemic for CCA to reduce mortality.

Keywords: Cholangiocarcinoma, Endemic, *Ophisthorchis Viverini*, Surveillance, Survival, Ultrasonography

Introduction

Cholangiocarcinoma (CCA) is the second most common primary liver cancer, accounting for 10-20% of all primary liver cancers[1]. In Western countries the main risk factors are primary sclerosing cholangitis (PSC) and liver cirrhosis, whereas in Asian countries the main risk factor is infestation by liver fluke[2]. Epidemiologically,cholangiocarcinomais far more common in Asia than in other parts of the world.Prevalenceis greatest in Southeast Asia, with a large burden of disease has been reported in Thailand where the population prevalence in the highest rate in north-eastern part reaches a level about 100 times higher than that in Western countries[3, 4].

Cholangiocarcinomais often initially silent and asymptomatic, resulting in late diagnosis. Thus the majority of cases are already in an unresectable stage at presentation and have poor responses to treatment. It is theorized that early detection may improve patient survival by increased detection of tumors when stillresectable. Although surveillance with ultrasound (US) of the liver may provide such early diagnosis, there is no solid proof of a survival benefit from such a program[5].

Surgical resection is the only treatment associated with prolonged disease-free survival. Unfortunately, this cancer's rapid growth and late detecton result in the majority of cases presenting at anadvanced unresectable stage with median survivals of only 9-12 months after non-surgical treatment [6-8].In contrast, with early-stage resectable tumors, the five-year survival after radical surgery is about 22-44 %[9] compared to unresectable tumors having a median survival within a year [6-8]. Detection of tumor in the early stage of malignancy may increase the opportunity for curative resection [and microscopically negative, surgical margins (R0).

Abdominal ultrasound surveillance may detect malignancies at an early-stage and thus increase the possibility of a surgical cure. Up to now there is no solid evidence to prove that there is a survival benefit from long-term US surveillance in apopulationresiding wherecholangiocarcinoma is endemic.Thus, this study aimed to compare survival outcomes between cholangiocarcinoma patientsdiagnosed through a program of surveillance by liver ultrasonography and patients who presented with cholangiocarcinoma before or outside the surveillance program.

## Methodology:

### Study design and population

The study was a comparison between patients who were not participants in the surveillance program and werediagnosed as having cholangiocarcinomaat the Chulabhorn Hospital, Bangkok, Thailand and CCA patients identified as part of a prospectivesurveillanceprogramin northern Thailand[10]. The study was approved by the the Ethics Committee for Human Research of the Chulabhorn Research Institute without need for informed consent in the non-surveillance group.

Patients in non surveillance cohort were patients who diagnosed as having cholangiocarcioma in Chulabhorn Hospital between April 2007 and November 2015. All were Thai adults, 30 years of age or older.

Patients in surveillance cohort were participants in an on–going, 5–year, population-based surveillance program in Banluang District, Nan Province, Thailand, a region which has been reported to have a high incidence of cholangiocarcinoma[10]. The surveillance program included abdominal ultrasound at enrollment and interval of every 6 months , measurement of tumor markers [CA 19-9, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP)] at

baseline. The study population consisted of 4225 adults (aged 30-60 years) indigenous to the area. The surveillance cohort consisted of those in the study population in whom cholangiocarcinoma was detected by this surveillance program during the approximately 4–year period from October, 2011 to November, 2015.

All patients in both cohorts who were suspected of having cholangiocarcinoma received contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) with or without additional magnetic resonance cholangiopancreatography (MRCP) for staging and assessment of surgical resectability. After staging, patient's information was brought to a multi-disciplinary institutional tumor board for determination of a plan of treatment.

The diagnoses of cholangiocarcinoma in both cohorts were based on tissue diagnosis usingeither a percutaneouscore needle biopsy or a liver resection specimen. Thecriteria for exclusion from the analysis for both cohortswerei)presence of coexisting malignancies, and ii) no follow-up information availableafter surgery.Staging ofcholangiocarcinomawas based on the American Joint Committee on Cancer (AJCC) criteria while resectabilty of the tumor was based on the Bismut-Correte Classification and major vascular encasement criteria [2]. Resected tumor margins werecategorized as one of the following: R0, all margins microscopically negative for tumor; R1,margin microscopically positive;R2, margin grossly positive for tumor.

After liver resection, patients were seen in follow-up at 1 month and every 3 months for the first year, then every 6 months for second and subsequent years. Recurrence was determined when imaging showed a new local nodule or mass, or distant metastasis. Information of patient's health status was based on review

of hospital records and the government death registry, as well as home calls by members of the project team.

**Statistical analysis**

Demographic data, type and anatomic location (premalignant lesion, intrahepatic type, hilar type, distal type) of CCA, TNM stage, resectability, positivity of resection margins (R0, R1, R2)[11], recurrence rate and survival were compared between the two cohorts. In the analysis, the primary outcome was survival benefit from abdominal ultrasound for cholangiocarcinomasurveillance. Secondary outcomes were resectability, margin-free resections, and recurrence.

We attempted to minimize lead time bias, which is defined as the time improvement of the survival due to early tumor detection by surveillance.

To calculate lead time bias by using specific tumor growth rate (TGR) multiplied by the difference of average tumour size in the surveillance and non-surveillance groups. Estimation of TGR was calculated by using data from four patients with intrahepatic cholangiocarcinoma who had available two pre-treatment CT/MRI studies at known dates, allowing measurement of the interval increase in tumor volume.

Then growth rate was calculated using equation [13]

$R = (f - f0) / (T - T0) \times 100$

Where T-T0 indicates the length of time between two measurement and f0-f indicates the maximum diameter at two points of measurement.

Unadjusted and adjusted overall survival curves by surveillance status were estimated by the Kaplan-Meier method. For the potential predictors of mortality, univariate and multivariate analyses were performed using the Cox regression model. A forward stepwise procedure utilized a significance defined as a p value less than 0.25 as the retention criteria. The analysis was conducted using SPSS version 20 (IBM Inc., New York, NY), and significance was defined as a 2-sided p value of less than 0.05.

Univariate and multivariate analyses with Cox proportional hazard model were used to determine the ability of variables to predict survival. The multivariate analysis was performed with forward stepwise selection to identify the independently predictive variables with $p< 0.1$ level of significance as a retention criterion. This analysis was performed with SPSS version 20.



## Results

Details of demographics, CCA types and staging, surgical resectability, tumor recurrence and survival are shown in Table 1. There were 192 patients in the non-surveillance group and 48 in the surveillance group, with mean ages of 60.8 and 53.0 years, respectively. CCA tumors in the surveillance group were smaller (4.02 cm vs 7.52 cm, $p<0.001$), in a lower cancer stage ($p < 0.001$), moreresectable (77.1% vs 11.5%, $p< 0.001$) and more often resected with tumor-free margins (R0, 97.3% vs 63.6%, $p < 0.001$) as compared with the non-surveillance group (Table 2). All14 premalignant lesions [6 biliary

intraepithelial neoplasia (Bil-IN) and 8 intraductal papillary neoplasm of the bile duct (IPNB)] were found in the surveillance group.

The surveillance cohort has significantly higher surgical respectability (77.1% vs 11.5%, p<0.001) and R0 resection rate (97.3% vs 63.6%) as compared with non-surveillance group.

Among patients with resected tumors found to have R0 margins, there was no significant difference in recurrence rate nor time to tumor recurrence (Table 2).The tumor growth rate, calculated using tumor growth information available from 4patients, was 2.05±0.54cm/100 days. This was used to calculate a adjusted lead time bias of 6.41 months. Survival was significantly longer in the surveillance than non-surveillance cohort (31.8 movs 6.7 mo,p <0.001, Table 2). This difference was independent of correction for lead time bias (Figure 1).

The univariate analysis evaluated factors for association with survival. Age, size of tumor, staging of CCA, operable stage, recurrence status, Child-Pugh classification, surveillance, albumin level, AST, ALT, ALP, total bilirubin and CA 19-9 were each found to be significantly associated with survival. Multivariate analysis revealed that the factors predicting survival receiving of ultrasound surveillance (Hazard Ratio (HR), 0.41; p =0.012), tumor considered resectable (HR, 0.11; p <0.001), and albumin level (HR, 0.39; p <0.001). The factors found to be predictive of mortality were largesize of tumor (HR, 1.09; p =0.001) and tumor recurrence (HR, 3.87; p =0.036) (Table3).

Discussion:

Liver flukes including *Opisthorchisviverrini*(OV) and *Clonorchissinensis* are consider Group 1 carcinogens according to the International Agency for Research on Cancer (IARC)[14].It is estimated that over 10 million people in Southeast Asian countries are infected with OV[15],and that about 6millionesofthem are in Thailand[16]. Thus OV infection remains a major health problem in Thailand and neighboring countries.Meanwhile *C.sinensis*impacts a larger area which includes Korea, China, Taiwan, Vietnam, and Russia, with more than 35 million people at risk of whom almost half are Chinese[17].With this severe endemic of liver flukes, cholangiocarcinoma is still be a major problem in many countries of Asia[4].

In Thailand, the incidenceof cholangiocarcinomais reported to rise starting about age 40 years and to peak about age 60[4].In our study, the majority of subjects detected by US surveillance to have cholangiocarcinomawere in their late 40s and early 50s. None were less than 40 years of age. Therefore, we recommend that US surveillance in endemic areas of Thailand be focused on adults aged 40 and above. Whether surveillance programs should have an upper age limit is unclear and will require further study.

Surveillance with ultrasound allows early detection of cholangiocarcinoma by detection of liver mass and/or bile duct dilatation.By ultrasound surveillance

pre-malignant lesions of CCA, including biliary intraepithelial neoplasia (Bil-IN) and intraductal papillary neoplasia of bile duct (IPN-B) in accordancewith the current WHO concept proposed by Nakanuma[18],could be found.

Surgical resection is currently the only treatment option for CCA patientswhich may be curative. A positive resection margin (non-R0 resection) is an indicator of a very poor prognosis[2]. This study showed a survival benefit for CCA patients who participated in an ultrasound surveillance program in a highly endemic area. Early detection alloweddiagnosis of CCA when it was potentiallyresectable with higher chance of obtainingtumor-free margins and prolongedimprove survival.

Even among patients with R0 resections,a third of cases in both groups eventuallyhave tumor recurrence. This reflects the aggressiveness of this cancer and that while negative resection margins predict longer survival they do not insure cure.

Surveillance in our study, however, was shown to independently predict improved survival. Many studies are trying to identify tools for early detection ofcholangiocarcinoma including serum tumour markers. These will be used to triage the patient for further investigationand includecarbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), interleukin-6 (IL-6), trypsinogen-2, mucin-5AC, and soluble fragment of cytokeratin 19 (CYFRA 21-1). Unfortunately, none of these markers have shown adequate sensitivity and specificity for CCA diagnosis [20].

In the setting of early CCA detection in non-PSC patients, serum tumor markers are likely to be less sensitive than reported in literature. In our surveillance cohort, serum CA 19-9, and CEA sensitivitieswere only 18.7% and

34.3%, respectively [10]. Further study for new tumor markers to assist CCA detection is needed to improve triage of patients at risk and help in the diagnosis of patients with liver malignancy. A side benefit of an US surveillance program is that its detection of more patients with CCA at an early stage will potentially make available a group whose blood/serum could be used to evaluate candidate tumor markers for their sensitivity in these earlier stages of carcinogenesis.

It is interesting that OV infestation produced chronic injury to bile duct epithelium, with resulting wound repair and excessive collagen deposition (periductal fibrosis) which can be identified on ultrasound as increased periductal echogenicity[23, 24] (figure). Further research of ultrasound findings, like periductal fibrosis, could help identify risks for future development of CCA and allow for close surveillance.

Our study has proved that there is survival benefit from ultrasound surveillance for cholangiocarcinoma in an endemic area, an increase from 6.7 to 31.8 months of median survival. However, interval US surveillance every 6 months for populatation in the edemic area is considered a huge workload. Further study is needed for cholangiocarcinoma risk stratification of population to target more specific high risk population to reduce number of population needed to be surveillance and potentially increase interval time of surveillance in lower risk population in the endemic area of cholangiocarcinoma.

Limitations:

There are limitations to this study, one of which is that the population who gained benefit from surveillance was in a highly endemic area of

cholangiocarcinoma where the main risk factor was from *Opisthorchis viverini* infestation. Therefore, the result may not directly apply to other regions where the etiology of cholangiocarcinoma is different.

## Conclusion:

Cholangiocarcinomaremains important cancer problem, especiallyin several parts of Asia where liver fluke infestations are endemic. Surveillance forcholangiocarcinoma in a population at risk in a highly endemic area was associated with survival benefit and should be considered to reduce mortality from this cancer.



## References :

[1] Altaee MY, Johnson PJ, Farrant JM, Williams R. Etiologic and clinical characteristics of peripheral and hilar cholangiocarcinoma. *Cancer*. 1991; **68**: 2051-5.

[2] Khan SA, Davidson BR, Goldin RD, *et al.* Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. *Gut*. 2012; **61**: 1657-69.

[3] Khan SA, Toledano MB, Taylor-Robinson SD. Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. *HPB (Oxford)*. 2008; **10**: 77-82.

[4] Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. *Semin Liver Dis*. 2004; **24**: 115-25.

[5] Braconi C, Patel T. Cholangiocarcinoma: new insights into disease pathogenesis and biology. *Infect Dis Clin North Am*. 2010; **24**: 871-84, vii.

[6] Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology*. 2001; **33**: 1353-7.

[7] Farley DR, Weaver AL, Nagorney DM. "Natural history" of unresected cholangiocarcinoma: patient outcome after noncurative intervention. *Mayo Clin Proc*. 1995; **70**: 425-9.

[8] Guglielmi A, Ruzzenente A, Campagnaro T, *et al.* Intrahepatic cholangiocarcinoma: prognostic factors after surgical resection. *World J Surg*. 2009; **33**: 1247-54.

[9] Gatto M, Alvaro D. New insights on cholangiocarcinoma. *World J Gastrointest Oncol*. 2010; **2**: 136-45.

[10] Sungkasubun P, Siripongsakun S, Akkarachinorate K, *et al.* Ultrasound screening for cholangiocarcinoma could detect premalignant lesions and early-stage diseases with survival benefits: a population-based prospective study of 4,225 subjects in an endemic area. *BMC Cancer*. 2016; **16**: 346.

[11] Oliveira IS, Kilcoyne A, Everett JM, Mino-Kenudson M, Harisinghani MG, Ganesan K. Cholangiocarcinoma: classification, diagnosis, staging, imaging features, and management. *Abdom Radiol (NY)*. 2017.

[12] Schwartz M. A biomathematical approach to clinical tumor growth. *Cancer*. 1961; **14**: 1272-94.

[13] Ozono S, Miyao N, Igarashi T, *et al.* Tumor doubling time of renal cell carcinoma measured by CT: collaboration of Japanese Society of Renal Cancer. *Jpn J Clin Oncol*. 2004; **34**: 82-5.

[14] Bouvard V, Baan R, Straif K, *et al.* A review of human carcinogens--Part B: biological agents. *Lancet Oncol*. 2009; **10**: 321-2.

[15] Sripa B, Bethony JM, Sithithaworn P, *et al.* Opisthorchiasis and Opisthorchis-associated cholangiocarcinoma in Thailand and Laos. *Acta Trop*. 2011; **120 Suppl 1**: S158-68.

[16] Jongsuksuntigul P, Imsomboon T. Opisthorchiasis control in Thailand. *Acta Trop*. 2003; **88**: 229-32.

[17] Keiser J, Utzinger J. Food-borne trematodiases. *Clin Microbiol Rev*. 2009; **22**: 466-83.

[18] Nakanuma Y, Sasaki M, Sato Y, Ren X, Ikeda H, Harada K. Multistep carcinogenesis of perihilar cholangiocarcinoma arising in the intrahepatic large bile ducts. *World J Hepatol*. 2009; **1**: 35-42.

[19] Wan XS, Xu YY, Qian JY, *et al.* Intraductal papillary neoplasm of the bile duct. *World journal of gastroenterology : WJG*. 2013; **19**: 8595-604.

[20] Gatto M, Bragazzi MC, Semeraro R, *et al.* Cholangiocarcinoma: update and future perspectives. *Dig Liver Dis*. 2010; **42**: 253-60.

[21] Goydos JS, Brumfield AM, Frezza E, Booth A, Lotze MT, Carty SE. Marked elevation of serum interleukin-6 in patients with cholangiocarcinoma: validation of utility as a clinical marker. *Ann Surg*. 1998; **227**: 398-404.

[22] Alvaro D. Serum and bile biomarkers for cholangiocarcinoma. *Curr Opin Gastroenterol*. 2009; **25**: 279-84.

[23] Sripa B, Brindley PJ, Mulvenna J, *et al.* The tumorigenic liver fluke Opisthorchis viverrini – multiple pathways to cancer. *Trends in parasitology*. 2012; **28**: 395-407.

[24] Chamadol N, Pairojkul C, Khuntikeo N, *et al.* Histological confirmation of periductal fibrosis from ultrasound diagnosis in cholangiocarcinoma patients. *J Hepatobiliary Pancreat Sci*. 2014; **21**: 316-22.

Table 1 demographic data of non-surveillance and surveillance patients.

| | Non surveillance (N=192) | Surveillance (N=48) | Total (N=240) | P value |
|---|---|---|---|---|
| Age (years) | 60.79±10.25 | 53.06±6.30 | 59.24 | <0.0001 |
| Mean tumor size (cm.) | 7.52±3.48 | 4.02±2.92 | 6.93 | 0.0001 |
| Gender | | | | 0.51 |
| Female | 73 (38.0%) | 21 (43.8%) | 94 | |
| Male | 119 (62.0%) | 27 (56.2%) | 146 | |
| Region of Thailand | | | | <0.0001 |
| North | 21 (10.9%) | 49 (100.0%) | 69 | |
| South | 5 (2.6%) | 0 | 5 | |
| East | 20 (10.4%) | 0 | 20 | |
| West | 3 (1.6%) | 0 | 3 | |
| Northeast | 58 (30.2%) | 0 | 58 | |
| Central | 85 (44.3%) | 0 | 85 | |
| Type by location of CCA | | | | <0.0001 |
| Premalignant lesion Bil-IN† and IPNB†† | 0 | 14 (29.8%) | 14 | |
| Intrahepatic | 130 (67.7%) | 22 (46.8%) | 152 | |
| Hilar | 53 (27.6%) | 6 (12.8%) | 59 | |
| Distal | 9 (4.7%) | 5 (10.6%) | 14 | |
| Staging AJCC | | | | <0.0001 |
| stage 0 (CIS) | 0 | 14 (29.2%) | 14 | |
| stage1 | 8 (4.2%) | 5 (10.4%) | 13 | |
| stage2 | 24 (12.5%) | 9 (18.8%) | 33 | |
| stage3 | 17 (8.8%) | 4 (8.3%) | 21 | |
| stage4 | 143 (74.5%) | 16 (33.3%) | 159 | |
| Received surgery | | | | <0.0001 |
| No | 170 (88.5%) | 11 (22.9%) | 181 | |
| Yes | 22 (11.5%) | 37 (77.1%) | 59 | |
| Recurrence | | | | <0.0001 |
| No | 183 (95.3%) | 35 (72.9%) | 218 | |
| Yes | 9 (4.7%) | 13 (27.1%) | 22 | |
| Death | | | | <0.0001 |
| No | 21 (10.9%) | 31 (64.6%) | 52 | |
| Yes | 171 (89.1%) | 17 (35.4%) | 188 | |

* CCA = cholangiocarcinoma CIS = Carcinoma In Situ

†Bil-IN = biliary intraepithelial neoplasia , ††IPNB= intraductal papillary neoplasm of of the bile duct

Table 2 Time to tumor recurrence and survival analysis of non surveillance and surveillance patients

| | Non surveillance | Surveillance | P value |
|---|---|---|---|
| Resectability | | | <0.001 |
| Unresectable | 170 (88.5%) | 11 (22.9%) | |
| Resectable | 22 (11.5%) | 37 (77.1%) | |
| Percent R0 resection* | | | <0.001 |
| R0 resection | 14 (63.6%) | 36 (97.3%) | |
| R1 resection | 8 (36.4%) | 1 (2.7%) | |
| R0 resection subgroup | | | |
| Percent recurrence | 5/14 (35.7%) | 12/36 (33.3%) | 1.000 |
| Median Time to recurrence | 52 months | 41 months | 0.926 |
| Mean Time to recurrence | 48.71 months | 34.75 months | |
| Overall survival | | | <0.001 |
| 1 year | 28.66% | 91.67% | |
| 2 year | 13.06% | 75.00% | |
| 3 year | 6.88% | 61.60% | |
| 4 year | 4.59% | 31.94% | |
| 5 year | 4.59% | NA | |
| Median survival in months | 6.73 | 38.2 (31.8†) | <0.001 |
| Mean survival in months | 12.12 | 36.54 | |

R0 resection = negative surgical resection margin , R1 = microscopic positive resection margin

†corrected lead time bias

**Table 3. Univariate and Multivariate Analysis of Factors Associated with survival**

| | Univariate Analysis | | | Multivariate Analysis* | | |
|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | ***p*-value** | **HR** | **95% CI** | ***p*-value** |
| Age (years) | 1.02 | 1.01-1.04 | 0.005 | | | |
| Gender (male vs female) | 1.10 | 0.81-1.47 | 0.548 | | | |
| Size (cm) | 1.14 | 1.10-1.19 | <0.001 | 1.09 | 1.04-1.15 | 0.001 |
| Staging | 1.84 | 1.56-2.18 | <0.001 | | | |
| Resectable | 0.12 | 0.08-0.19 | <0.001 | 0.11 | 0.03-0.35 | <0.001 |
| Recurrence | 0.47 | 0.28-0.76 | 0.002 | 3.87 | 1.09-13.76 | 0.036 |
| Child-Pugh classification | | | | | | |
| B vs A | 3.23 | 2.26-4.64 | <0.001 | | | |
| C vs A | 4.41 | 2.54-7.66 | <0.001 | | | |
| Surveillance vs non Surveillance | 0.17 | 0.11-2.88 | <0.001 | 0.41 | 0.20-0.82 | 0.012 |
| Albumin (g/dL) | 0.29 | 0.22-0.39 | <0.001 | 0.39 | 0.25-0.62 | <0.001 |
| ALT (U/L)† | 1.24 | 1.10-1.40 | <0.001 | | | |
| AST (U/L)† | 1.6 | 1.40-1.83 | <0.001 | | | |
| Alkaline phosphatase (IU/L)† | 1.65 | 1.47-1.87 | <0.001 | | | |
| Total Bililubin (mg/dL) | 1.05 | 1.03-1.07 | <0.001 | | | |
| CA19-9 > 37 U/ml. | 2.49 | 1.77-3.50 | <0.001 | | | |

*Laboratory results were gained at first visit

†per log2 increase

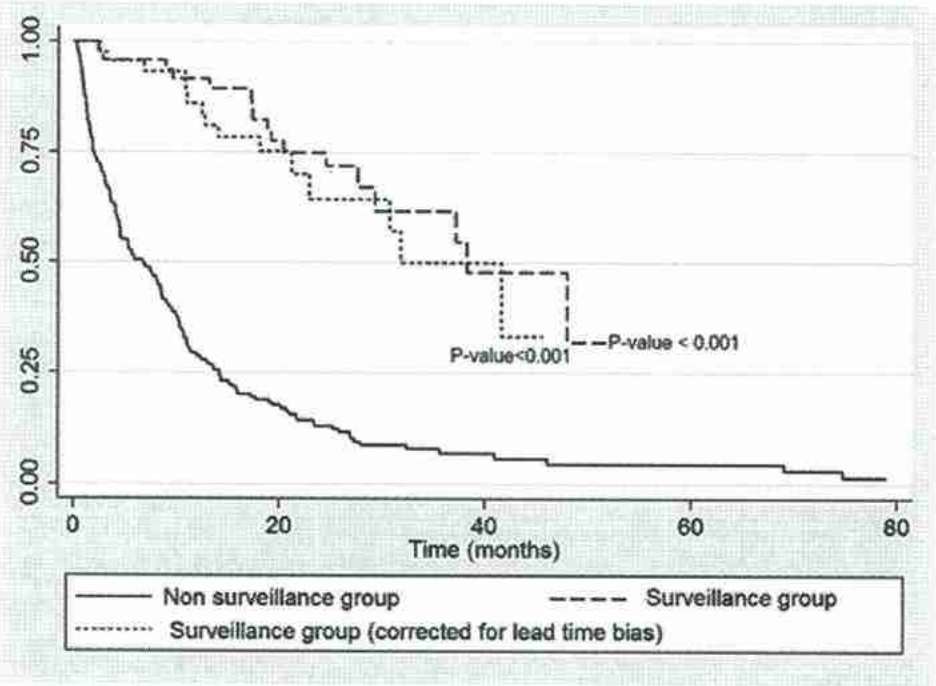


Fig 2a - transverse ultrasonography scan of left hepatic lobe showing normal periportal echogenicity around left portal vein.

51x37mm (300 x 300 DPI)

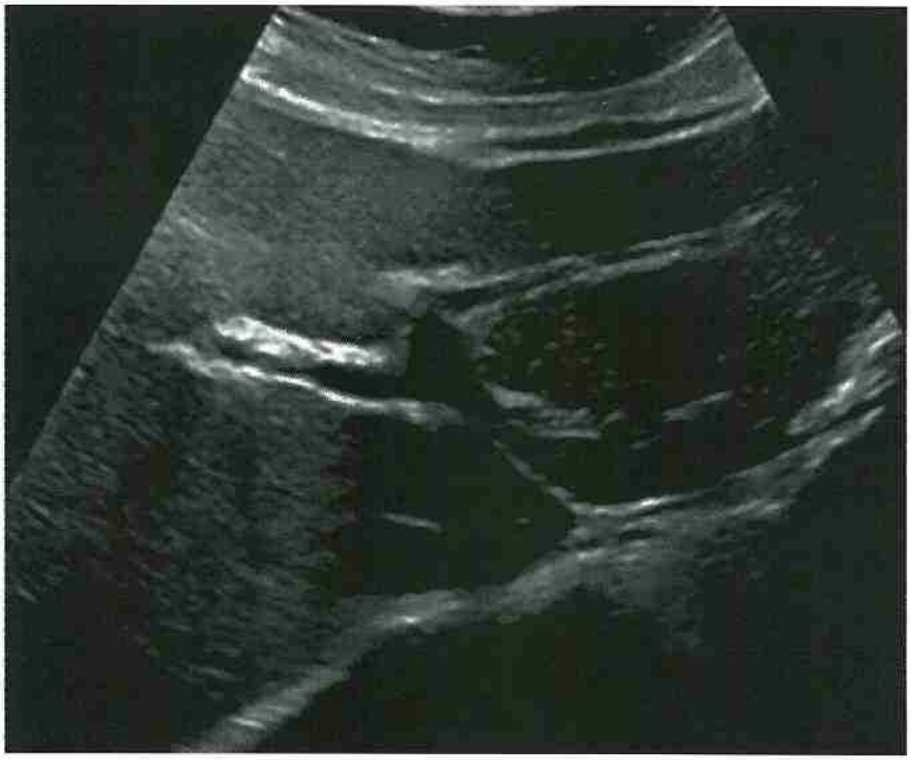

Fig 2A - transverse ultrasonography scan of left hepatic lobe showing normal periportal echogenicity around left portal vein.

42x33mm (300 x 300 DPI)

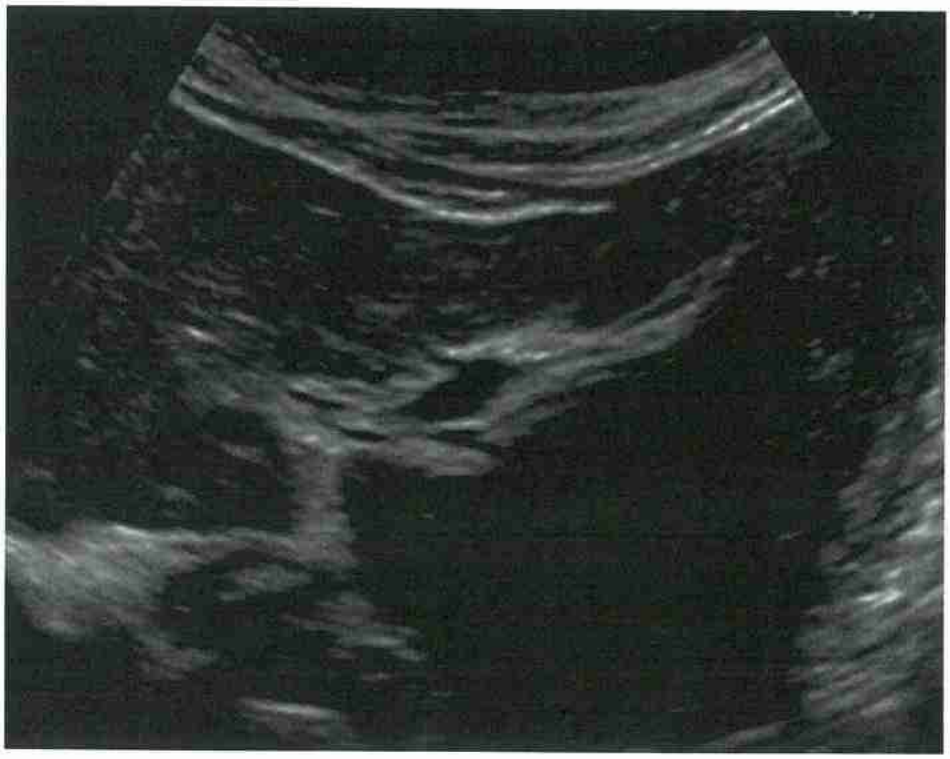

Fig 2B - transverse ultrasonography scan of left hepatic lobe showing showing increase periportal/ductal echogenicity (periductal fibrosis) with visible left intrahepatic bile duct along with left portal vein.

42x33mm (300 x 300 DPI)