Surveillance for Cholangiocarcinoma in Patients with Primary Sclerosing Cholangitis - Effective and Justified?

Nataliya Razumilava[1]
Gregory J. Gores[2]

[1]Division of Gastroenterology, University of Michigan, Ann Arbor, MI, USA; [2]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA.

Running Title: CCA surveillance in PSC

Key Words: cholangiography, fluorescence in situ hybridization, FISH, liver transplantation

Address for Correspondence: Gregory J. Gores, MD
Professor of Medicine and Physiology
College of Medicine Mayo Clinic
200 First Street SW
Rochester, Minnesota 55905
Tel: 507 284 0686
Fax: 507 284 0762
E-mail: gores.gregory@mayo.edu

List of Abbreviations: CA 19-9, carbohydrate antigen 19-9; CCA, cholangiocarcinoma; ERC, endoscopic retrograde cholangiography; FISH, fluorescent *in situ* hybridization; MRC, magnetic resonance cholangiography; MRI, magnetic resonance imaging; OLT, orthotopic liver transplantation; PSC, primary sclerosing cholangitis

This work was supported by NIH Grants DK59427 (GJG)

Number of
Pages: 9
Title characters: 98
Words without references: 1322
References: 12
Tables: 2
Figures: 2

The aim of cancer surveillance is **to detect cancer or precancerous lesions** in **asymptomatic, high risk** individuals when **cancer is more likely to be prevented or cured**.(1) This is a highly germane topic for physicians taking care of primary sclerosing cholangitis (PSC) patients.

The etiology of PSC is unknown and there are currently no effective therapeutic strategies to prevent adverse outcomes of this progressive liver disease. Malignancies are the cause of death in up to 44% of patients with PSC.(2) The risk for cholangiocarcinoma (CCA) development in PSC patients is approximately 160-1,560 fold greater than the general population.(3) The absolute risk of CCA in PSC is approximately 9% over 10 years.(4) The mean age of CCA diagnosis in PSC patients is in the fourth decade of life versus the seventh decade in the general population. Hence, given the increased risk of CCA in young adults with PSC, the question is frequently posed: Should surveillance strategies be employed to detect early CCA in PSC patients and if so, how? Unfortunately, a data-driven, surveillance policy for CCA in patients with PSC does not yet exist (Table 1). The position of the American Association for Study of Liver Diseases is that "in the absence of evidence based information, many clinicians screen patients with an imaging study plus a CA 19-9 at annual intervals."(5) The European Association for the Study of Liver Diseases states "there is no evidence-based approach for surveillance of development of biliary malignancies, but endoscopic retrograde cholangiography (ERC) with brush cytology (and/or biopsy) sampling is recommended when clinically indicated. In the absence of an evidence-based strategy, many clinicians use imaging modalities [ultrasound, magnetic resonance imaging (MRI)] in combination with CA19-9 at annual intervals."(6) Per the American College of Gastroenterology,

"surveillance for CCA with regular (every 6–12 months) cross-sectional imaging with ultrasound or MR and serial CA 19-9 measures is recommended by experts in this area, for all patients with PSC."(7) Thus, even societal guidelines differ on this topic.

Surveillance for CCA in PSC - Effective?

To make surveillance effective, the following criteria should be met: 1) there should be a defined population at risk; 2) testing modalities and treatment for early-stage disease are available, affordable, and acceptable to the individual and jurisdiction of interest; 3) the process is cost-effective and standardized; and 4) there are patient survival benefits if cancer is detected early. In the following paragraphs we will examine these surveillance criteria in the context of PSC (Table 2).

We do not understand which PSC patients are at risk for developing CCA. Several environmental and genetic factors have been proposed but none have been convincingly confirmed in follow-up studies. The duration of associated inflammatory bowel disease and colectomy for colonic neoplasia may identify a subset of PSC patients at high risk for developing CCA,(8) but even this observation needs confirmation. Among PSC patients diagnosed with CCA, about 50% will be found to have CCA within two years of PSC diagnosis. This observation suggests that patients with newly diagnosed PSC maybe at the highest risk for a CCA diagnosis. However, these data maybe confounded by an ascertainment bias, namely early symptomatic albeit undiagnosed CCA has brought their PSC to medical attention. Nonetheless, if a surveillance strategy is cost-effective, the incidence of CCA in PSC (1.5% per year)(9) is likely sufficient to justify surveillance as it is approximately the same cut-off incidence for hepatocellular carcinoma in cirrhosis (1.5-2%) used to justify surveillance in that patient population.

Magnetic resonance cholangiography (MRC) combined with magnetic resonance imaging (MRI), ERC, and serum biomarker, carbohydrate antigen 19-9 (CA 19-9) are the most accepted modalities for CCA surveillance in PSC (Fig. 1). MRI/MRC has 89% sensitivity and 76% accuracy in CCA diagnosis. The CA 19-9 level ≥20 U/mL enhances MRI/MRC sensitivity to 100% at the expense of the specificity (38%) and accuracy (47%). Biliary brushings obtained by ERC for conventional cytology and/or fluorescence in situ hybridization (FISH) analysis which detects chromosomal alterations (polysomy is an equivalent of aneuploidy) are valuable complementary tests. FISH sensitivity for detection of perihilar CCA is 38-58% as compared with 15% sensitivity for conventional cytology. In PSC patients the combination of CA 19-9 ≥129 U/mL and polysomy was found to be predictive of cancer (HR 10.92; P <.001), and presence of either of them associated with cancer diagnosis within 2 years.(10) As an ideal surveillance modality should have high sensitivity and specificity and be non-invasive, in our opinion, ERCP does not fit the bill being too invasive and fraught with complications (e.g., pancreatitis, cholangitis), having limited performance due to the paucicellular nature of cytologic specimens, and will miss mass lesions not associated with the large bile duct involvement. CA19-9 can't be used alone as it is not specific for CCA and can be elevated with bacterial cholangitis, other gastroenterological and gynecological cancers, and smoking. Additionally, more than 30% of PSC patients with CA 19-9 ≥129 U/mL are free of cancer long-term. CA 19-9 utility will be influenced by the Lewis blood group phenotype (7% of the population are Lewis negative and have the undetectable CA 19-9 level)(9) and by allelic variants of fucosyltransferases 2 and 3.(11) Ultrasound sensitivity for CCA detection in PSC is very limited. Traditionally, CCA thought to be a slowly

growing tumor, but its doubling time to guide surveillance intervals is unknown and hard to define in PSC patients who most often have non-mass forming perihilar CCA. Cost-effectiveness of PSC-CCA surveillance and extend of lead and length time bias are unknown, and affordability depends on the jurisdiction and personal resources. Nonetheless, MRI/MRC and determination of serum CA 19-9 values are non-invasive and can be used to prompt more invasive and specific studies such as ERC with brush cytology.

Surveillance for CCA in PSC - Justified?

If an early CCA is identified in a PSC patient – Do we have effective therapy? Surgical resection for CCA is associated with a 5-year survival rate of <30% even in non-PSC patients who potentially have better baseline liver function. However, neoadjuvant chemoirradiation therapy followed by orthotopic liver transplantation (OLT) available in highly specialized centers is a curative treatment option with 5-year survival >70% for the subset of PSC patients with early perihilar CCA. Liver transplantation outcomes for early perihilar CCA are identical with those for hepatocellular carcinoma for which surveillance policies are well-accepted. The protocol for this approach employing chemoirradiation plus liver transplantation is resource intensive and not universally available. For example, in the event of non-resectable CCA diagnosis, 37% of transplant centers would perform OLT with neoadjuvant therapy, 33% would resort to palliative treatment, and the remaining 30% would make an outside referral.(12)

PSC is a rare disease often complicated by infection and cholestasis requiring urgent imaging and intervention. It would be unfeasible to conduct randomized controlled trials on a proper surveillance strategy, as the control group would inevitably be contaminated

by imaging studies based on clinical need. Hence, it is unlikely if the cost-effectiveness of surveillance for CCA in PSC patients will ever be settled by a prospective, randomized trial.

Surveillance for CCA in PSC – What Do Experienced Clinicians Do?

Patients seek medical attention, to alleviate current and future suffering, and to prolong life. Physicians must respond to these individual goals within the confines of an individual, unique patient-physician relationship, not on the basis of abstract population outcomes. Physicians and patients should participate in shared decision making. In this context, PSC patients should be informed of their cancer risk, the availability of surveillance strategies, and how positive results would be managed. If the patient opts for surveillance, the authors recommend MRI/MRC combined with serum CA 19-9 level on an annual basis. If a dominant biliary stricture and/or rise in CA 19-9 >129 U/mL are observed, an ERC with biliary brushings for conventional and cytological examination should be obtained. A patient with early stage perihilar tumor should be evaluated for liver transplantation and referred to a specialized center if deemed to be an acceptable candidate (Fig. 2).

REFERENCES

1. Sullivan T, Sullivan R, Ginsburg OM: Screening for Cancer: Considerations for Low- and Middle-Income Countries. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, eds. Cancer: Disease Control Priorities, Third Edition (Volume 3). Washington (DC), 2015.
2. Razumilava N, Gores GJ, Lindor KD. Cancer surveillance in patients with primary sclerosing cholangitis. Hepatology 2011;54:1842-1852.
3. Singal AK, Stanca CM, Clark V, Dixon L, Levy C, Odin JA, Fiel MI, et al. Natural history of small duct primary sclerosing cholangitis: a case series with review of the literature. Hepatol Int 2011;5:808-813.
4. Claessen MM, Vleggaar FP, Tytgat KM, Siersema PD, van Buuren HR. High lifetime risk of cancer in primary sclerosing cholangitis. J Hepatol 2009;50:158-164.
5. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology 2010;51:660-678.
6. Wiencke K, Boberg KM. Current consensus on the management of primary sclerosing cholangitis. Clin Res Hepatol Gastroenterol 2011;35:786-791.
7. Lindor KD, Kowdley KV, Harrison ME, American College of G. ACG Clinical Guideline: Primary Sclerosing Cholangitis. Am J Gastroenterol 2015;110:646-659; quiz 660.
8. Gulamhusein AF, Eaton JE, Tabibian JH, Atkinson EJ, Juran BD, Lazaridis KN. Duration of Inflammatory Bowel Disease Is Associated With Increased Risk of Cholangiocarcinoma in Patients With Primary Sclerosing Cholangitis and IBD. Am J Gastroenterol 2016.
9. Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet 2014;383:2168-2179.
10. Barr Fritcher EG, Voss JS, Jenkins SM, Lingineni RK, Clayton AC, Roberts LR, Halling KC, et al. Primary sclerosing cholangitis with equivocal cytology: fluorescence in situ hybridization and serum CA 19-9 predict risk of malignancy. Cancer Cytopathol 2013;121:708-717.
11. Bonato G, Cristoferi L, Strazzabosco M, Fabris L. Malignancies in Primary Sclerosing Cholangitis - A Continuing Threat. Dig Dis 2015;33 Suppl 2:140-148.
12. Trilianos P, Selaru F, Li Z, Gurakar A. Trends in pre-liver transplant screening for cholangiocarcinoma among patients with primary sclerosing cholangitis. Digestion 2014;89:165-173.

TABLE LEGEND

Table 1. Summary of societal guidelines for CCA surveillance in PSC. CA 19-9, carbohydrate antigen 19-9; CCA, cholangiocarcinoma; ERC, endoscopic retrograde cholangiography; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis

Table 2. Principles of disease surveillance and its applicability to surveillance of CCA in patients with PSC. CA 19-9, carbohydrate antigen 19-9; CCA, cholangiocarcinoma; MRC, magnetic resonance cholangiography; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis

FIGURE LEGEND

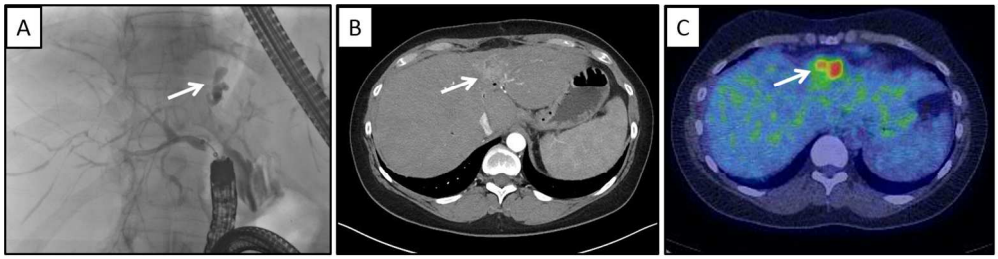
Figure 1. Cholangiocarcinoma (CCA) in a 51 year old asymptomatic female with primary sclerosing cholangitis and an elevated CA 19-9. A: ERC, the white arrow demonstrated segmental bile duct obstruction worrisome for CCA in this context; B: MRI, the white arrow denotes a mass lesion; C: Positron emission tomography, the white arrow demonstrates avid uptake of ^{18}F-FDG consistent with a malignancy

Figure 2. Teaching points on surveillance of CCA in PSC. CA 19-9, carbohydrate antigen 19-9; CCA, cholangiocarcinoma; ERC, endoscopic retrograde cholangiography; FISH, fluorescent *in situ* hybridization; MRC, magnetic resonance cholangiography; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis

Figure 2

- Cost-effectiveness of CCA surveillance in patients with PSC is unknown
- Due to rarity of PSC the clinical trial assessing cost-effectiveness of CCA surveillance is unlikely be feasible
- 50% of patients with newly diagnosed PSC who will develop CCA are diagnosed with CCA within first two years since PSC diagnosis and therefore should be aggressively screened for this cancer
- Non-invasive MRI/MRC and CA 19-9 with a cutoff ≥129 U/mL are preferable surveillance modalities for CCA in PSC patients
- ERC should be reserved for patients with abnormal MRI/MRC and CA 19-9 findings and combined with FISH cytological evaluation for polysomy or performed when clinically indicated (i.e., jaundice development)
- PSC patients with early perihilar CCA should be referred to the specialized center for potential liver transplantation

Criteria for a successful surveillance strategy	Met or not
Defined population at risk	Yes - Patients with PSC
Available, affordable, acceptable surveillance modalities	Yes - Annual MRI/MRC with CA 19-9
Available, affordable, acceptable treatment modalities	Yes, but very limited - Resection for early disease with well compensated liver function - Neoadjuvant chemoirradiation followed by liver transplantation for early perihilar CCA in highly specialized centers
Cost-effectiveness of the process	Unknown - As the annual incidence rate of CCA in PSC is 1.5% and is comparable with incidence of hepatocellular carcinoma, surveillance might be justified
Standardization of the process	None
Patient survival benefits	Yes - Benefits are limited to patients with early perihilar disease treated with neoadjuvant chemoirradiation followed by liver transplantation in highly specialized centers



Cholangiocarcinoma (CCA) in a 51 year old asymptomatic female with primary sclerosing cholangitis and an elevated CA 19-9. A: ERC, the white arrow demonstrated segmental bile duct obstruction worrisome for CCA in this context; B: MRI, the white arrow denotes a mass lesion; C: Positron emission tomography, the white arrow demonstrates avid uptake of 18F-FDG consistent with a malignancy
161x42mm (300 x 300 DPI)

Professional society	Recommendations
The American Association for Study of Liver Diseases	“Inadequate information exists regarding the utility of screening for CCA in PSC; in the absence of evidence based information, many clinicians screen patients with an imaging study plus a CA 19-9 at annual intervals.” “We recommend evaluation for CCA in patients with deterioration of their constitutional performance status or liver biochemical-related parameters .”
The European Association for the Study of Liver Diseases	“There is currently no evidence-based screening strategy for CCA in PSC, and no general recommendations for surveillance can be given. ERC with brush cytology (and/or biopsy) is recommended when clinically indicated (deterioration of clinical status and/or biochemical liver tests or recognition of a dominant stricture). In the absence of an evidence-based strategy, many clinicians use imaging modalities (ultrasound, MRI) in combination with CA 19-9 at annual intervals.”
The American College of Gastroenterology	“Consider screening for CCA with regular cross-sectional imaging with ultrasound or MR and serial CA 19-9 every 6–12 months. ”